

FORM P-1390 (Modified)  
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

**5941-01-DRK**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

**10/009611**

INTERNATIONAL APPLICATION NO.  
**PCT/US00/15071**

INTERNATIONAL FILING DATE  
**31 May 2000**

PRIORITY DATE CLAIMED  
**10 June 1999**

TITLE OF INVENTION

**METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS**

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
  - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ has been communicated by the International Bureau.
  - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
  - a. ☐ is attached hereto.
  - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
  - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
  - b. ☐ have been communicated by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

**Published Specification, WO 00/76489**

Express Mail No. EF378134357US

U.S. APPLICATION NO. 10/009611 PCT/US00/15071		INTERNATIONAL APPLICATION NO. ATTORNEY'S DOCKET NUMBER 5941-01-DRK		
24. The following fees are submitted: <b>BASIC NATIONAL FEE ( 37 CFR 1.492 (a) (1) - (5) ) :</b> <input checked="" type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO ..... \$1040.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... \$890.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$740.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) ..... \$100.00 <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b> \$1,040.00		<b>CALCULATIONS PTO USE ONLY</b>		
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30		\$0.00		
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	43 - 20 =	23	x \$18.00	
Independent claims	16 - 3 =	13	x \$84.00	
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>			\$0.00	
<b>TOTAL OF ABOVE CALCULATIONS =</b>			<b>\$2,546.00</b>	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.			\$0.00	
<b>SUBTOTAL =</b>			<b>\$2,546.00</b>	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492 (f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30			\$0.00	
<b>TOTAL NATIONAL FEE =</b>			<b>\$2,546.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>			\$0.00	
<b>TOTAL FEES ENCLOSED =</b>			<b>\$2,546.00</b>	
			Amount to be: refunded	\$
			charged	\$
a. <input type="checkbox"/> A check in the amount of _____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>23-0455</u> in the amount of <u>\$2,546.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>23-0455</u> A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. <b>WARNING:</b> Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.				
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.				
SEND ALL CORRESPONDENCE TO:				
David R. Kurlandsky Registration No. 41,505  Warner-Lambert Company 2800 Plymouth Road Ann Arbor, MI 48105 Tel. (734) 622-7304 Fax (734) 622-1553		David R. Kurlandsky SIGNATURE  David R. Kurlandsky NAME  41,505 REGISTRATION NUMBER  07 December 2001 DATE		

METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION  
AND IMAGING AMYLOID DEPOSITS

FIELD OF THE INVENTION

5 This invention relates to a method of inhibiting amyloid protein aggregation and imaging amyloid deposits. More particularly, this invention relates to a method of inhibiting amyloid protein aggregation in order to treat Alzheimer's disease.

BACKGROUND OF THE INVENTION

10 Amyloidosis is a condition characterized by the accumulation of various insoluble, fibrillar proteins in the tissues of a patient. The fibrillar proteins that comprise the accumulations or deposits are called amyloid proteins. While the particular proteins or peptides found in the deposits vary, the presence of fibrillar morphology and a large amount of  $\beta$ -sheet secondary structure is common to many types of amyloids. An amyloid deposit is formed by the aggregation of  
15 amyloid proteins, followed by the further combination of aggregates and/or amyloid proteins.

The presence of amyloid deposits has been shown in various diseases, each with its particular associated protein, such as Mediterranean fever, Muckle-Wells syndrome, idiopathic myeloma, amyloid polyneuropathy, amyloid  
20 cardiomyopathy, systemic senile amyloidosis, amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Alzheimer's disease, Down's syndrome, Scrapie, Creutzfeldt-Jacob disease, Kuru, Gerstmann-Straussler-Scheinker syndrome, medullary carcinoma of the thyroid, Isolated atrial amyloid,  $\beta_2$ -microglobulin amyloid in dialysis patients, inclusion body myositis,  
25  $\beta_2$ -amyloid deposits in muscle wasting disease, Sickle Cell Anemia, Parkinson's Disease, and Islets of Langerhans diabetes Type II insulinoma.

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Alzheimer's disease is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgement, and emotional stability that gradually leads to mental deterioration and ultimately death. Because Alzheimer's disease and related degenerative brain disorders are a major medical issue for an increasingly aging population, the need for new treatments and methods for diagnosing the disorders are needed.

A simple, noninvasive method for detecting and quantitating amyloid deposits in a patient has been eagerly sought. Presently, detection of amyloid deposits involves histological analysis of biopsy or autopsy materials. Both methods have major drawbacks. For example, an autopsy can only be used for a postmortem diagnosis.

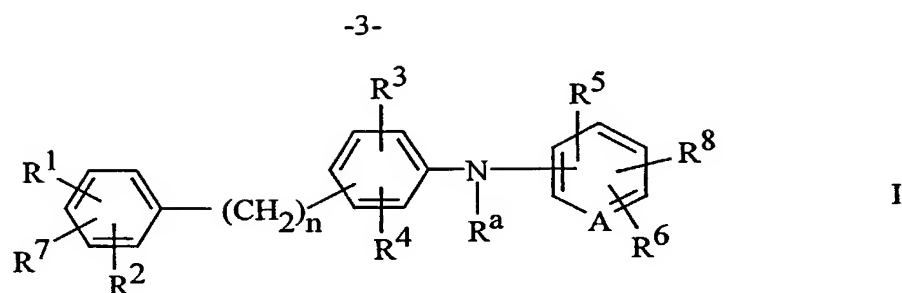
The direct imaging of amyloid deposits in vivo is difficult, as the deposits have many of the same physical properties (i.e., density and water content) as normal tissues. Attempts to image amyloid deposits directly using magnetic resonance imaging (MRI) and computer-assisted tomography (CAT) have been disappointing and have detected amyloid deposits only under certain favorable conditions. In addition, efforts to label amyloid deposits with antibodies, serum amyloid P protein, or other probe molecules has provided some selectivity on the periphery of tissues, but has provided for poor imaging of tissue interiors.

Thus, it would be useful to have a noninvasive technique for imaging and quantitating amyloid deposits in a patient. In addition, it would be useful to have compounds that inhibit the aggregation of amyloid proteins to form amyloid deposits.

## SUMMARY OF THE INVENTION

The present invention provides a method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



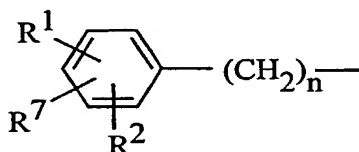


wherein

- 5  $R^a$  is hydrogen,  $C_1$ - $C_6$  alkyl, or  $-CC_1$ - $C_6$  alkyl;  
 $n$  is 0 to 5 inclusive;  
 $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are independently hydrogen, halogen,  
 $-OH$ ,  $-NH_2$ ,  $NR^bR^c$ ,  $-CO_2H$ ,  $-CO_2C_1$ - $C_6$  alkyl,  $-NO_2$ ,  $-OC_1$ - $C_{12}$   
 $alkyl$ ,  $-C_1$ - $C_8$  alkyl,  $-CF_3$ ,  $-CN$ ,  $-OCH_2$  phenyl,  $-OCH_2$ -substituted  
10 phenyl,  $-(CH_2)_m$ -phenyl,  $-O$ -phenyl,  $-O$ -substituted phenyl,  
 $-CH=CH$ -phenyl,  $-O(CH_2)_pNR^bR^c$ ,  $-CNR^bR^c$ ,  $-NHCR^b$ ,  
 $-NH(CH_2)_pNR^bR^c$ ,  $-N(C_1$ - $C_6$ alkyl) $(CH_2)_pNR^bR^c$ ,  
15  $\begin{array}{c} \text{CH}_2OC_1-C_6 \text{ alkyl} \\ | \\ -CH \\ | \\ \text{CH}_2OC_1-C_6 \text{ alkyl} \end{array}$  ;  
 $R^8$  is  $COOH$ , tetrazolyl,  $-SO_2R^d$ , or  $-CONHSO_2R^d$ ;  
 $R^b$  and  $R^c$  are independently hydrogen,  $-C_1$ - $C_6$  alkyl,  $-(CH_2)_m$ -phenyl, or  
 $R^b$  and  $R^c$  taken together with the nitrogen atom to which they are  
attached form a cyclic ring selected from piperidinyl, pyrrolyl,  
20 imidazolyl, piperazinyl, 4- $C_1$ - $C_6$  alkylpiperazinyl, morpholino,  
thiomorpholino, decahydroisoquinoline, or pyrazolyl;  
 $R^d$  is hydrogen,  $-C_1$ - $C_6$  alkyl,  $-CF_3$ , or phenyl;  
 $m$  is 0 to 5 inclusive;  
 $p$  is 1 to 5 inclusive;  
25  $A$  is  $CH$  or  $N$ ;

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$R^1$  and  $R^2$ , when adjacent to one another, can be methylene-dioxy;  
or the pharmaceutically acceptable salts thereof.

In a preferred embodiment, the  group is attached at  
the 4-position of the phenyl ring.

5 In a preferred embodiment of the method, in the compounds of Formula I

$R^a$  is hydrogen;

$n$  is 2; and

$R^3$  and  $R^4$  are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

10  $R^a$  is hydrogen;

$R^1$  is halo;

$R^2$  is hydrogen or halo;

$R^3$ ,  $R^4$ ,  $R^5$ , and  $R^6$  are hydrogen; and

$n$  is 2 to 5 inclusive.

15 In another preferred embodiment of the method, in the compounds of Formula I

$R^a$  is hydrogen;

$n$  is 2 or 3;

$R^1$  is  $-NR^bR^c$ ; and

$R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , and  $R^7$  all are hydrogen.

20 In a preferred embodiment of the method, in the compounds of Formula I

$R^a$  is hydrogen;

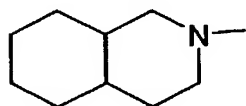
$n$  is 2;

$R^3$  and  $R^4$  are hydrogen; and

$R^1$ ,  $R^2$ , and  $R^7$  are independently chlorine,  $-N(CH_2CH_3)_2$ ,  $-OH$ ,  $CH_3$ -,

25 fluorine,  $-CF_3$ , phenyl, hydrogen,  $-OCH_2$  phenyl,

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-O(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -O phenyl, -O(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>,-CH(CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, pyrrolyl, -CH=CH-phenyl,, -N[(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>]<sub>2</sub>, substituted phenyl,-OCH<sub>2</sub>-substituted phenyl, pyrrolozyl, or -N(phenyl)<sub>2</sub>.

5 In a preferred embodiment of the method, in the compounds of Formula I

R<sup>a</sup> is hydrogen;

n is 3, 4, or 5;

R<sup>3</sup> and R<sup>4</sup> are hydrogen; andR<sup>1</sup>, R<sup>2</sup>, and R<sup>7</sup> are independently chlorine or hydrogen.

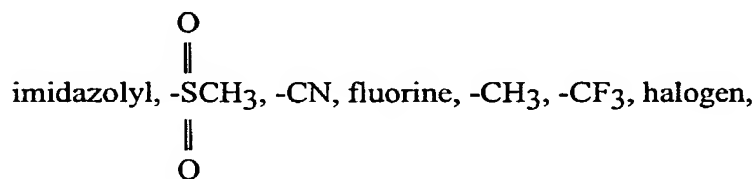
10 In a preferred embodiment of the method, in the compounds of Formula I

R<sup>a</sup> is hydrogen;

n is 2;

R<sup>3</sup> and R<sup>4</sup> are hydrogen; andR<sup>5</sup>, R<sup>6</sup>, and R<sup>8</sup> are independently hydrogen, -CO<sub>2</sub>H, -NO<sub>2</sub>, -OCH<sub>3</sub>,

15



20

-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -NH<sub>2</sub>, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

R<sup>a</sup> is hydrogen;

n is 2;

R<sup>3</sup> and R<sup>4</sup> are hydrogen; and

25

R<sup>5</sup> is -CO<sub>2</sub>H.













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2-{4-[2-(4-[2-Diethylaminoethylamino]phenyl)ethyl]phenylamino}-  
benzoic acid;

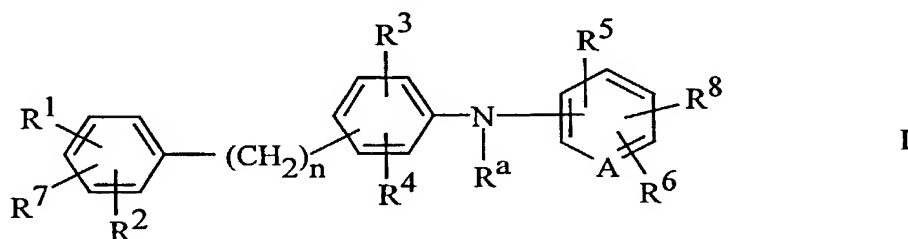
2-{4-[3-(4-Morpholinophenyl)propyl]phenylamino}-benzoic acid;

2-{4-[3-(4-Piperazinylphenyl)propyl]phenylamino}-benzoic acid; and

2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid.

The invention also provides the foregoing compounds wherein the benzoic acid portion is replaced with a pyridyl carboxylic acid, for example, 4-[4-(3,4-dichlorophenyl)phenylamino]-3-hydroxycarbonylpyridine.

Also provided is a method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



wherein

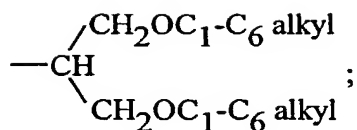
$\text{Ra}$  is hydrogen,  $\text{C}_1\text{-C}_6$  alkyl, or  $\text{-CC}_1\text{-C}_6$  alkyl;  
 $n$  is 0 to 5 inclusive;

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6$ , and  $\text{R}^7$  are independently hydrogen, halogen,

$\text{-OH}$ ,  $\text{-NH}_2$ ,  $\text{NR}^{\text{bRc}}$ ,  $\text{-CO}_2\text{H}$ ,  $\text{-CO}_2\text{C}_1\text{-C}_6$  alkyl,  $\text{-NO}_2$ ,  $\text{-OC}_1\text{-C}_{12}$  alkyl,  $\text{-C}_1\text{-C}_8$  alkyl,  $\text{-CF}_3$ ,  $\text{-CN}$ ,  $\text{-OCH}_2$  phenyl,  $\text{-OCH}_2$ -substituted phenyl,  $\text{-(CH}_2\text{)}_m\text{-phenyl}$ ,  $\text{-O-phenyl}$ ,  $\text{-O-substituted phenyl}$ ,

$\text{-CH=CH-phenyl}$ ,  $\text{-O(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$ ,  $\text{-CNR}^{\text{bRc}}$ ,  $\text{-NHCR}^{\text{b}}$ ,  
 $\text{-NH(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$ ,  $\text{-N(C}_1\text{-C}_6\text{alkyl)(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$ ,

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R<sup>8</sup> is COOH, tetrazolyl, -SO<sub>2</sub>R<sup>d</sup>, or -CONHSO<sub>2</sub>R<sup>d</sup>;

R<sup>b</sup> and R<sup>c</sup> are independently hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, or

5 R<sup>b</sup> and R<sup>c</sup> taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C<sub>1</sub>-C<sub>6</sub> alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R<sup>d</sup> is hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -CF<sub>3</sub>, or phenyl;

m is 0 to 5 inclusive;

10 p is 1 to 5 inclusive;

A is CH or N;

R<sup>1</sup> and R<sup>2</sup>, when adjacent to one another, can be methylene-dioxy; or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of the method, in the compounds of Formula I

15 R<sup>a</sup> is hydrogen;  
n is 2; and  
R<sup>3</sup> and R<sup>4</sup> are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

20 R<sup>a</sup> is hydrogen;  
R<sup>3</sup> and R<sup>4</sup> are hydrogen; and  
n is 2 to 5 inclusive.

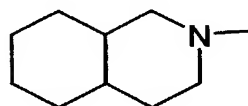
In a preferred embodiment of the method, in the compounds of Formula I

25 R<sup>a</sup> is hydrogen;  
n is 2;  
R<sup>3</sup> and R<sup>4</sup> are hydrogen; and

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R<sup>1</sup>, R<sup>2</sup>, and R<sup>7</sup> are independently chlorine, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -OH, CH<sub>3</sub>-,  
fluorine, -CF<sub>3</sub>, phenyl, hydrogen, -OCH<sub>2</sub> phenyl,  
-O(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -O phenyl, -O(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>,  
-CH(CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, pyrrolyl, -CH=CH-phenyl,

5



, -N[(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>]<sub>2</sub>, substituted phenyl,

-OCH<sub>2</sub>-substituted phenyl, pyrazolyl, or -N(phenyl)<sub>2</sub>.

In a preferred embodiment of the method, in the compounds of Formula I

R<sup>a</sup> is hydrogen;

n is 3, 4, or 5;

10

R<sup>3</sup> and R<sup>4</sup> are hydrogen; and

R<sup>1</sup>, R<sup>2</sup>, and R<sup>7</sup> are independently chlorine or hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R<sup>a</sup> is hydrogen;

n is 2;

15

R<sup>3</sup> and R<sup>4</sup> are hydrogen; and

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, -CO<sub>2</sub>H, -NO<sub>2</sub>, -OCH<sub>3</sub>,

imidazolyl, -CN, fluorine, -CH<sub>3</sub>, -CF<sub>3</sub>, halogen,

-NH-C<sub>1</sub>-C<sub>6</sub> alkyl, -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, -NH<sub>2</sub>, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

20

R<sup>a</sup> is hydrogen;

n is 2;

R<sup>3</sup> and R<sup>4</sup> are hydrogen; and

R<sup>5</sup> is -CO<sub>2</sub>H.

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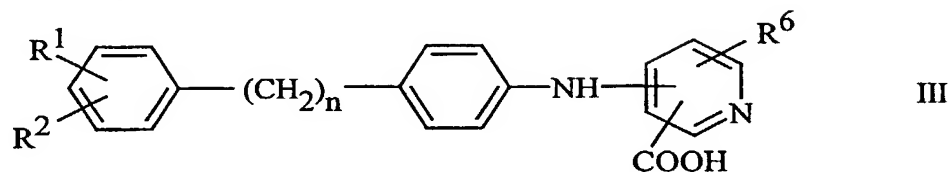
Also provided is a preferred method of inhibiting the aggregation of  
amyloid proteins to form amyloid deposits, the method comprising administering



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n and R<sup>6</sup> are as defined above in Formula I.

Another preferred group of compounds have Formula III



and pharmaceutically acceptable salts thereof,

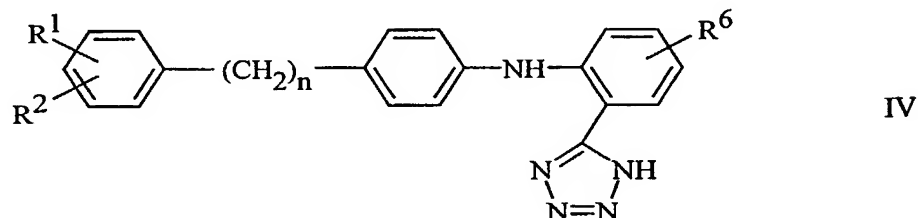
wherein:

R<sup>1</sup> is halo;

R<sup>2</sup> is H or halo; and

n and R<sup>6</sup> are as defined above in Formula I.

Another group of preferred invention compounds have Formula IV



and pharmaceutically acceptable salts thereof,

wherein:

R<sup>1</sup> is halo;

R<sup>2</sup> is H or halo; and

n and R<sup>6</sup> are as defined above in Formula I.

In a preferred embodiment of the method, the novel compounds of Formula I are provided which are

2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

- 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;  
 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-  
 5-nitrobenzoic acid;  
 2-{4-[2-[-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;  
 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;  
 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;  
 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic  
 acid;  
 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;  
 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;  
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;  
 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;  
 2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic  
 acid;  
 2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;  
 5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;  
 2-(4-Phenethyl-phenylamino)-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic  
 acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic  
 acid;  
 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-  
 benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-  
 benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

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- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;  
 5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic  
 acid;  
 5 6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic  
 acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic  
 10 acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic  
 acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-  
 15 benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-  
 benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-  
 benzoic acid;  
 20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic  
 acid;  
 2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-  
 benzoic acid;  
 25 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-  
 phenylamino)-benzoic acid;  
 30 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

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- 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic  
 acid;  
 5 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-  
 benzoic acid;  
 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-  
 10 benzoic acid;  
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;  
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;  
 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic  
 acid; or  
 15 2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

The present invention also provides the compounds:

- 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino} benzoic acid;  
 20 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;  
 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic acid;  
 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 25 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-  
 5-nitrobenzoic acid;  
 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid;  
 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;  
 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic  
 acid;  
 30 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;  
 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;





- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;
- 2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

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2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic  
acid;

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-  
benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

10 2-{4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenylamino}-benzoic  
acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino} benzoic acid;

15 2-{4-[3-(4-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Aminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino} benzoic acid

monohydrochloride;

20 2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino} benzoic acid  
monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino} benzoic acid;

25 2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic  
acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino} benzoic acid;

30 2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;

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2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride;

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride;

5        2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(3-Acetylaminophenyl)propyl]]phenylamino}benzoic acid;  
2-{4-[3-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride;

10       2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride;

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-(1H-Pyrrol-1-yl)phenyl)propyl]phenylamino}benzoic acid;  
15       2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid;  
20       2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid;  
2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid;  
2-{4-[3-(3-Piperidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid;  
5-{[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-

thioxothiazolidin-3-yl}acetic acid;

25       5-{[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-  
thioxothiazolidin-3-yl}acetic acid;

3-{5-{[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-  
thioxothiazolidin-3-yl}propanoic acid;

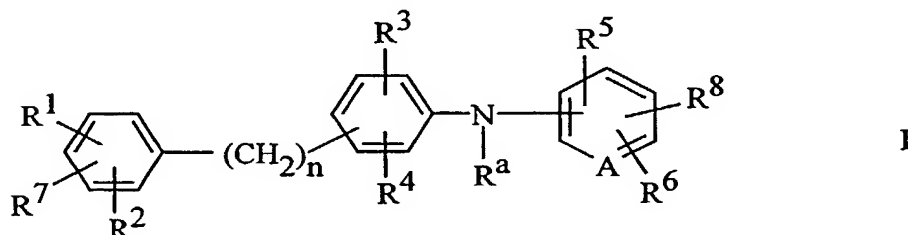
4-{5-{[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-  
30       thioxothiazolidin-3-yl}butanoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.



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- a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



wherein

$R^a$  is hydrogen,  $C_1$ - $C_6$  alkyl, or  $-CC(=O)-C_6$  alkyl;

$n$  is 0 to 5 inclusive;

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are independently hydrogen,

halogen, -OH, -NH<sub>2</sub>,  $NR^bR^c$ , -CO<sub>2</sub>H, -CO<sub>2</sub> $C_1$ - $C_6$  alkyl, -NO<sub>2</sub>, -OC<sub>1</sub>- $C_{12}$  alkyl, - $C_1$ - $C_8$  alkyl, -CF<sub>3</sub>, -CN, -OCH<sub>2</sub> phenyl, -OCH<sub>2</sub>-substituted phenyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl, -O(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>, -C(=O)NR<sup>b</sup>R<sup>c</sup>, -NHCR<sup>b</sup>, -NH(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>, -N( $C_1$ - $C_6$ alkyl)(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>,

$\begin{array}{c} \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \\ | \\ \text{---CH} \\ | \\ \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \end{array}$  ;

$R^8$  is COOH, tetrazolyl, -SO<sub>2</sub>R<sup>d</sup>, or -CONHSO<sub>2</sub>R<sup>d</sup>;

$R^b$  and  $R^c$  are independently hydrogen, - $C_1$ - $C_6$  alkyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, or  $R^b$  and  $R^c$  taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4- $C_1$ - $C_6$

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alkylpiperazinyl, morpholino, thiomorpholino,  
decahydroisoquinoline, or pyrazolyl;

R<sup>d</sup> is hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -CF<sub>3</sub>, or phenyl;

m is 0 to 5 inclusive;

5 p is 1 to 5 inclusive;

A is CH or N;

R<sup>1</sup> and R<sup>2</sup>, when adjacent to one another, can be methylene-dioxy;  
or the pharmaceutically acceptable salts thereof;

10 b. allowing sufficient time for the labeled compound to become  
associated with amyloid deposits; and

c. detecting the labeled compound associated with the amyloid  
deposits.

In a preferred embodiment of the method, the patient has or is suspected to have  
Alzheimer's disease.

15 In a preferred embodiment of the method, the labeled compound is a radio labeled  
compound.

In a preferred embodiment of the method, the labeled compound is detected using  
MRI.

The present invention also provides the preferred compounds:

20 2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;  
2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;  
2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic  
acid;  
25 2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid;  
and pharmaceutical formulations thereof.

Pharmaceutically acceptable acid addition salts, amides, and prodrugs of the  
foregoing compounds are also provided by this invention.

# DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" means a straight or branched chain hydrocarbon having from 1 to 12 carbon atoms. Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, sec-butyl, pentyl, hexyl, octyl, decyl, and 1,1-dimethyloctyl.

Preferred alkyl groups are C<sub>1</sub>-C<sub>8</sub> alkyl, and especially C<sub>1</sub>-C<sub>6</sub> alkyl.

The term "alkoxy" means an alkyl group attached to an oxygen atom. Representative examples of alkoxy groups include methoxy, ethoxy, tert-butoxy, propoxy, and isobutoxy. Preferred alkoxy groups are C<sub>1</sub>-C<sub>12</sub> alkoxy, and especially C<sub>1</sub>-C<sub>6</sub> alkoxy.

The term "halogen" includes chlorine, fluorine, bromine, and iodine.

The term "substituted" means that one or more hydrogen atom in a molecule has been replaced with another atom or group of atoms. For example, substituents include halogen, especially chloro, -OH, -CF<sub>3</sub>, -NO<sub>2</sub>, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>6</sub>alkyl), -N(C<sub>1</sub>-C<sub>6</sub>alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>6</sub> alkyl, -OC<sub>1</sub>-C<sub>6</sub> alkyl, -CN, -CF<sub>3</sub>, -CO<sub>2</sub>H, and -CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl.

The term "substituted phenyl" means a phenyl ring in which from 1 to 4 hydrogen atoms have been independently replaced with a substituent, preferably one selected from the list above. Typical "substituted phenyl" groups include 4-chlorophenyl, 3,4-dibromophenyl, 3-fluoro-4-methylphenyl, 3,4-dichlorophenyl, 3,4-methylenedioxyphenyl, and 4-dimethylaminophenyl.

The symbol "-" means a covalent bond.

Substituent groups represented by R<sup>1</sup>, R<sup>3</sup>, and R<sup>5</sup>, for example, include amino(NR<sup>b</sup>R<sup>c</sup>) and acylamino (-NHCOR<sup>b</sup>). R<sup>b</sup> and R<sup>c</sup> can be hydrogen, alkyl and phenylalkyl and substituted phenylalkyl, and typical NR<sup>b</sup>R<sup>c</sup> groups include methylamino, diethylamino, isobutyl-propylamino, benzylamino, and 3,4-dimethoxybenzylamino. Examples of acylamino groups include formamido, acetamido, 2-phenylacetamido, and 2-(3-nitrophenyl)acetamido. R<sup>1</sup>, R<sup>3</sup>, and R<sup>5</sup> can also be aminoalkoxy (-O(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>) such as N-methylaminomethoxy and 2-(N-benzylamino)ethoxy, as well as



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aminoalkylamino ( $-\text{NH}(\text{CH}_2)_p\text{NR}^b\text{R}^c$ ) such as 3-(dimethylamino)propylamino and 2-(N-ethyl-N-benzylamino)ethylamino. Substituent groups such as  $\text{R}^1$ ,  $\text{R}^3$ , and  $\text{R}^5$  additionally can be cyclic structures, for instance when  $\text{NR}^b\text{R}^c$  is part of the substituent group, and  $\text{R}^b$  and  $\text{R}^c$  are taken together with the nitrogen to which they are attached to form a cyclic ring selected from imidazole, pyrrole, piperidine, piperazine, 4- $\text{C}_1$ - $\text{C}_6$  alkylpiperazine, morpholine, thiomorpholine, pyrazole, and decahydroisoquinoline.

Substituent groups such as  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^5$ ,  $\text{R}^6$ , and  $\text{R}^7$  also can be  $-\text{CH}=\text{CH}$ -phenyl (i.e., styryl), phenoxy, O-substituted phenyl such as 3-iodophenoxy, 2,4,6-trihydroxyphenoxy, 2-fluoro-3-nitrophenoxy, as well as -O-benzyl and -O-substituted benzyl such as 2-trifluoromethylbenzyloxy and 4-aminobenzyloxy.

The term "pharmaceutically acceptable salt, ester, amide, and prodrug" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laureate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as, nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for

example, Berge S.M., et al., *Pharmaceutical Salts*, *J. Pharm. Sci.*, 66:1-19 (1977) which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, nontoxic esters of the compounds of this invention include C<sub>1</sub>-C<sub>6</sub> alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C<sub>5</sub>-C<sub>7</sub> cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C<sub>1</sub>-C<sub>4</sub> alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods, for example by reacting a carboxylic acid of Formula I with an alcohol such as ethanol or benzyl alcohol.

Examples of pharmaceutically acceptable, nontoxic amides of the compounds of this invention include amides derived from ammonia, primary C<sub>1</sub>-C<sub>6</sub> alkyl amines and secondary C<sub>1</sub>-C<sub>6</sub> dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C<sub>1</sub>-C<sub>3</sub> alkyl primary amides and C<sub>1</sub>-C<sub>2</sub> dialkyl secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds, as well as mixture thereof, including racemic mixtures, form part of this invention.



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example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

5 Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable nonirritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the  
10 active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be required. Ophthalmic formulations,  
15 eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

In a preferred embodiment of the invention, the labeled compound is introduced into a patient in a detectable quantity and after sufficient time has passed for the compound to become associated with amyloid deposits, the labeled  
20 compound is detected noninvasively inside the patient. In another embodiment of the invention, a labeled compound of Formula I is introduced into a patient, sufficient time is allowed for the compound to become associated with amyloid deposits, and then a sample of tissue from the patient is removed and the labeled compound in the tissue is detected apart from the patient. In a third embodiment  
25 of the invention, a tissue sample is removed from a patient and a labeled compound of Formula I is introduced into the tissue sample. After a sufficient amount of time for the compound to become bound to amyloid deposits, the compound is detected.

The administration of the labeled compound to a patient can be by a  
30 general or local administration route. For example, the labeled compound may be administered to the patient such that it is delivered throughout the body. Alternatively, the labeled compound can be administered to a specific organ or tissue of interest. For example, it is desirable to locate and quantitate amyloid

deposits in the brain in order to diagnose or track the progress of Alzheimer's disease in a patient.

The term "tissue" means a part of a patient's body. Examples of tissues include the brain, heart, liver, blood vessels, and arteries. A detectable quantity is a quantity of labeled compound necessary to be detected by the detection method chosen. The amount of a labeled compound to be introduced into a patient in order to provide for detection can readily be determined by those skilled in the art. For example, increasing amounts of the labeled compound can be given to a patient until the compound is detected by the detection method of choice. A label is introduced into the compounds to provide for detection of the compounds.

The term "patient" means humans and other animals. Those skilled in the art are also familiar with determining the amount of time sufficient for a compound to become associated with amyloid deposits. The amount of time necessary can easily be determined by introducing a detectable amount of a labeled compound of Formula I into a patient and then detecting the labeled compound at various times after administration.

The term "associated" means a chemical interaction between the labeled compound and the amyloid deposit. Examples of associations include covalent bonds, ionic bonds, hydrophilic-hydrophilic interactions, hydrophobic-hydrophobic interactions, and complexes.

Those skilled in the art are familiar with the various ways to detect labeled compounds. For example, magnetic resonance imaging (MRI), positron emission tomography (PET), or single photon emission computed tomography (SPECT) can be used to detect radiolabeled compounds. The label that is introduced into the compound will depend on the detection method desired. For example, if PET is selected as a detection method, the compound must possess a positron-emitting atom, such as  $^{11}\text{C}$  or  $^{18}\text{F}$ .

Another example of a suitable label in a compound of Formula I is an atom such as  $^{13}\text{C}$ ,  $^{15}\text{N}$ , or  $^{19}\text{F}$  which can be detected using magnetic resonance imaging (MRI) which is also sometimes called nuclear magnetic resonance (NMR). In addition, the labeled compounds of Formula I may also be detected by MRI using paramagnetic contrast agents.



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The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is sufficient. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any manner.

## EXAMPLES

### SYNTHESIS

Compounds of Formula I can be prepared by several routes as illustrated in Schemes 6 through 9. Schemes 1 through 5 show synthetic routes that can be used to obtain the desired starting amines (IV), (VIII), (XV), and (XXI).

In Scheme 1, the appropriately substituted aldehyde (I) and a nitrophenylacetic acid (II) yield olefin (III) when heated in piperidine at 150°C. Standard hydrogenation conditions, such as Raney nickel, give desired amine (IV).

Scheme 2 depicts the synthesis of amine (VIII) which contains a three methylene tether. Condensation of aldehyde (I) and nitro-ketone (V) in the presence of sodium hydroxide gives the desired alpha, beta-unsaturated ketone, which upon standard hydrogenation conditions (Raney nickel) gives (VII) and then Wolff-Kishner conditions yields the desired amine (VIII).

Scheme 3 is very similar to Scheme 2, except that the aldehyde (I) is condensed with a substituted aniline (IX).

Scheme 4 illustrates standard Wittig conditions in which the starting materials (XII) and (XIII) are obtained via aldol condensation and ylide chemistry, respectively. Reaction of aldehyde (XII) and bromophosphorane (XIII) in the



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presence of a base, such as butyl lithium, gives diene (XIV). Standard reduction conditions (e.g., Raney nickel) of (XIV) yields the desired amine (XV).

Scheme 5 illustrates the synthesis of amine (XXI) which contains a 5-methylene tether. Wittig reaction of the bromophosphorane (XVII), which is formed from the corresponding substituted bromide (XVI), and nitro aldehyde (XIX), obtained from Swern oxidation of the corresponding alcohol (XVIII), using a base (e.g., LHDMS) yields olefin (XX). Reduction of (XX) using standard conditions (Raney nickel) gives amine (XXI).

Scheme 6 illustrates one route to obtain compounds of Formula I. Either by Buchwald coupling (Method A) followed by saponification or utilizing the Ullman reaction (Method B), compounds of Formula I can be isolated from amines such as (IV), (VIII), and (XV). Compounds of Formula I that contain hydroxy groups, such as Examples 4 and 6, require demethylation of the hydroxy protecting groups with reagents such as boron tribromide in the final step of the synthesis.

Protecting groups will also be used when reactive functional groups such as amino and carboxylic acids are present, so as to avoid unwanted side reactions. Carboxy groups typically are converted to esters (e.g., tert-butyl, benzyl), and amino groups generally are acylated (e.g., acetyl or trimethylsilyl). These and other such protecting groups are well-known to organic chemists, and are fully described by Greene and Wuts in Protective Groups in Organic Synthesis, John Wiley and Sons, New York (2<sup>nd</sup> Ed. 1991). All citations are incorporated herein by reference.

Scheme 7 illustrates the synthesis of compounds of Formula I by reacting amines such as (IV), (VIII), and (XXI) with fluoro-nitro intermediate (XXIV), in the presence of a base (e.g., LHMDs or Et<sub>3</sub>N) to give ester (XXV). This ester can then be saponified using standard conditions, such as sodium hydroxide.

In Scheme 8, amine (XV) can be coupled with readily available fluoro-substituted carboxylic acids [e.g., (XXVI) or (XXVII)] in the presence of various bases (such as DBU or triethylamine) to yield compounds of Formula I.

Scheme 9 depicts coupling of amine (VIII) with readily available methyl ester (XXVIII) in the presence of a base, such as imidazole, to give ester (XXIX).

This ester can then be saponified as usual to give compounds of Formula I.

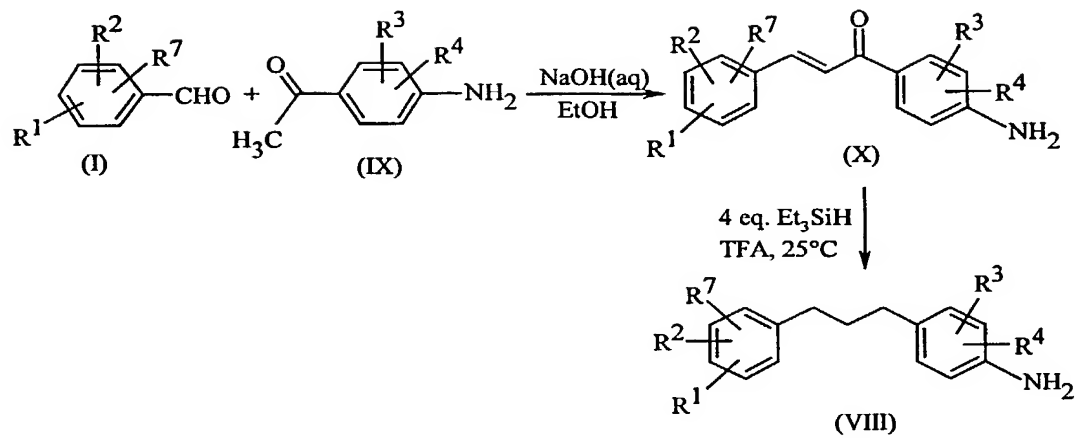
Scheme 10 illustrates the synthesis of fluoro-intermediate (XXIV) which is obtained by nitration of readily available methyl ester (XXX) to give (XXVIII). Treatment of (XXVIII) with potassium cyanide gives (XXIV).

5 In Scheme 11, the synthesis of compounds related to Example 18 is illustrated. Reaction of the potassium salts of ortho-substituted benzoic acids (XXVI) with substituted anilines (XXVII) in the presence of potassium carbonate and cupric acetate yields various iodo-substituted aminobenzoic acids (XXVIII). Reaction of (XXVIII) with substituted boronic acids and palladium chloride gives  
10 the desired substituted aminobenzoic acids (XXX).

It should, of course, be recognized that several invention compounds of Formula I can be prepared from other compounds defined by Formula I, utilizing standard organic reactions such as oxidation, reduction, alkylation, condensation, elimination, and similar well-known synthetic processes. For example,

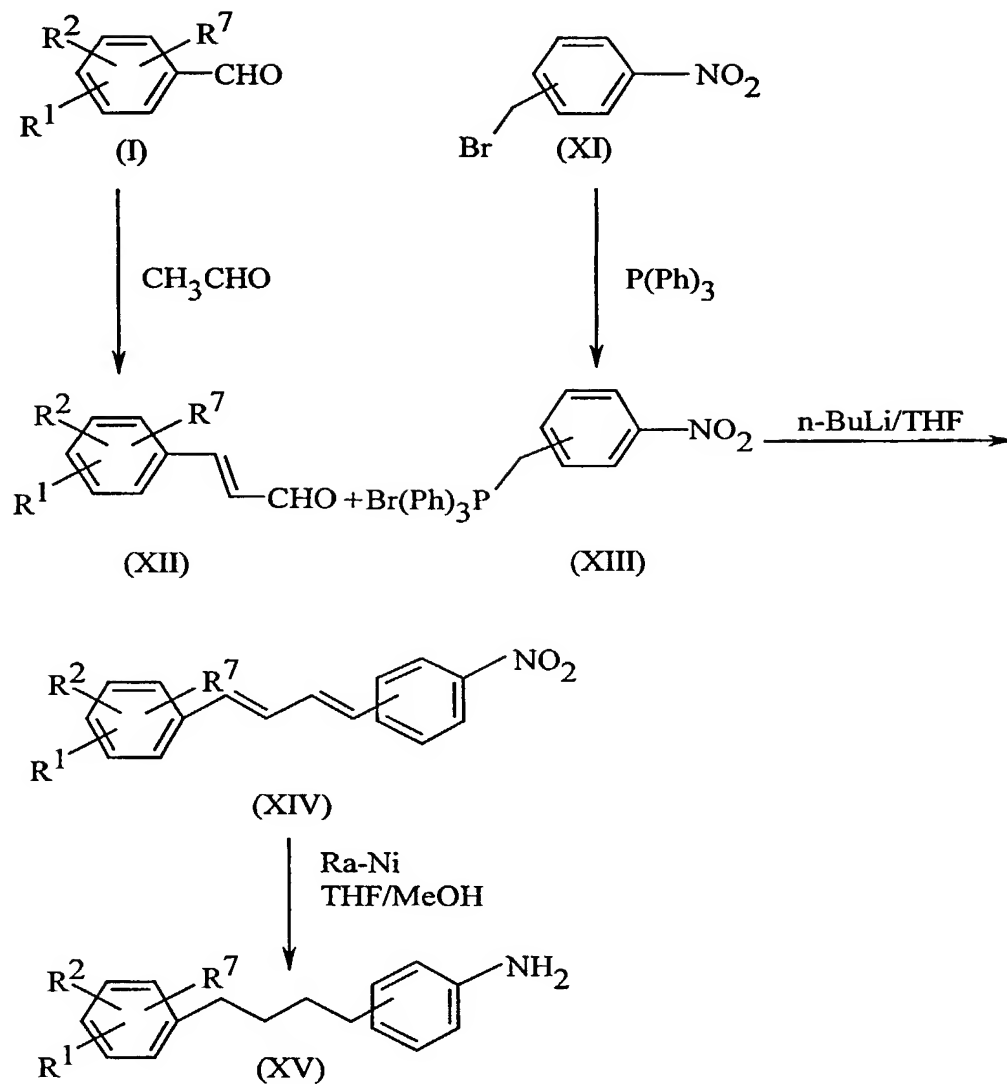
15 compounds of Formula I wherein  $R^a$  is hydrogen are readily alkylated to form compounds wherein  $R^a$  is  $C_1$ - $C_6$  alkyl. Compounds wherein  $R^1$  is  $NH_2$  are readily acylated by reaction with an acid halide or acid anhydride to provide compounds wherein  $R^1$  is  $-NHCOR^b$ . Similarly, compounds wherein  $R^1$  is  $NO_2$  are easily reduced to provide compounds wherein  $R^1$  is  $NH_2$ . The benzoic acids  
20 (where  $R^8$  is  $COOH$ ) are readily converted to esters and amides, as well as salts and other prodrugs by routine processes. For example, the benzoic acid can be reacted with oxalylchloride to form the acid chloride, which then readily reacts with a sulfonamide such as methanesulfonamide to produce the corresponding invention compound where  $R^8$  is  $-CONHSO_2CH_3$ .





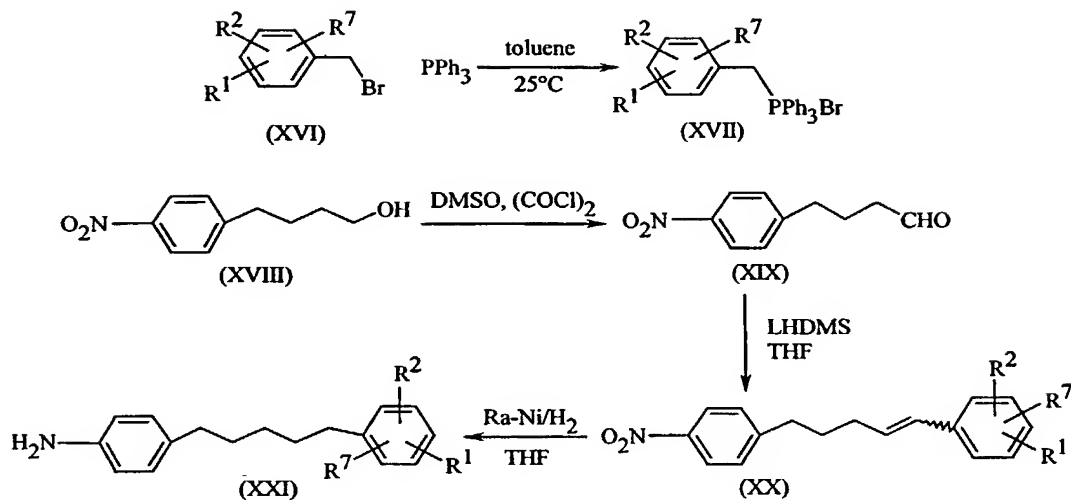
-39-

Scheme 4



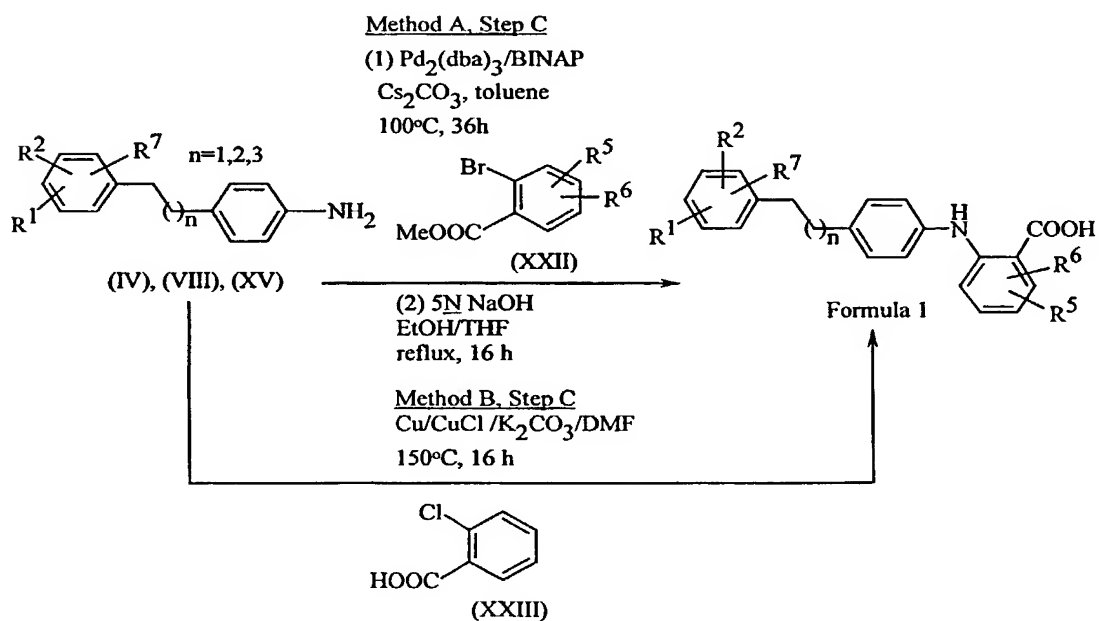
-40-

Scheme 5



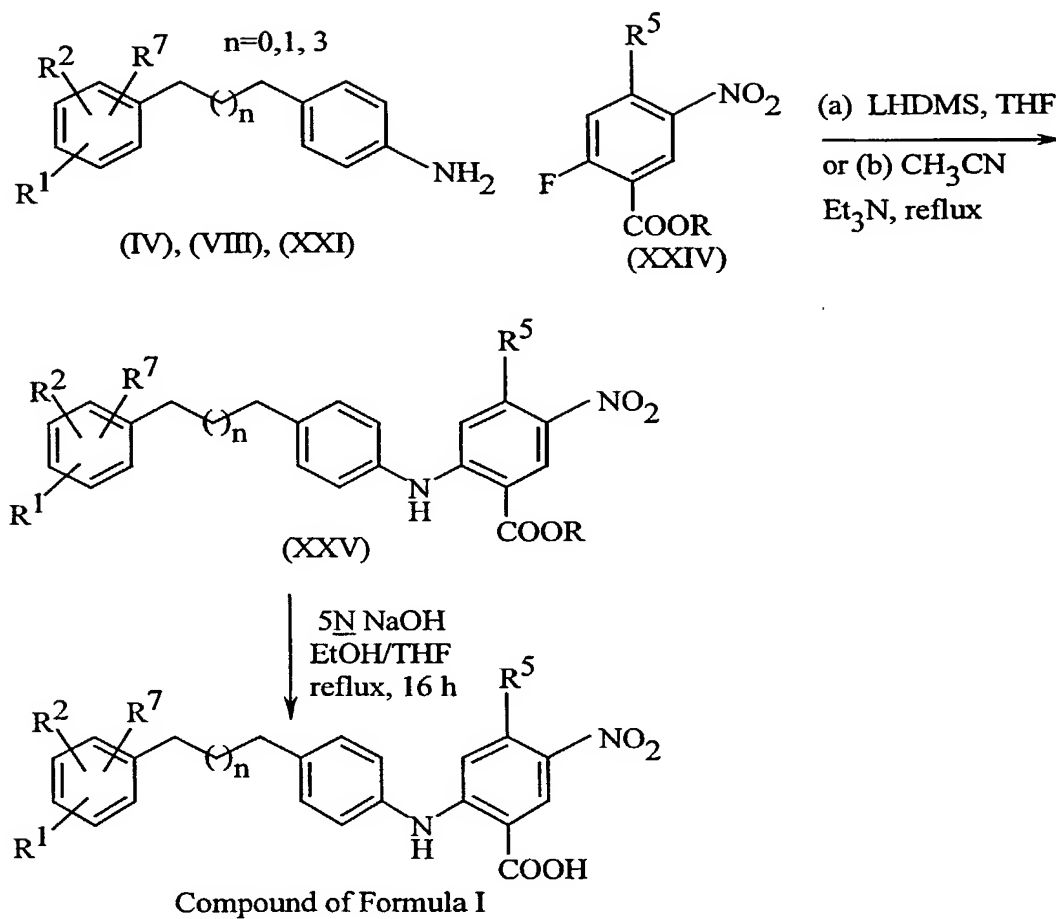
## Coupling Routes

Scheme 6



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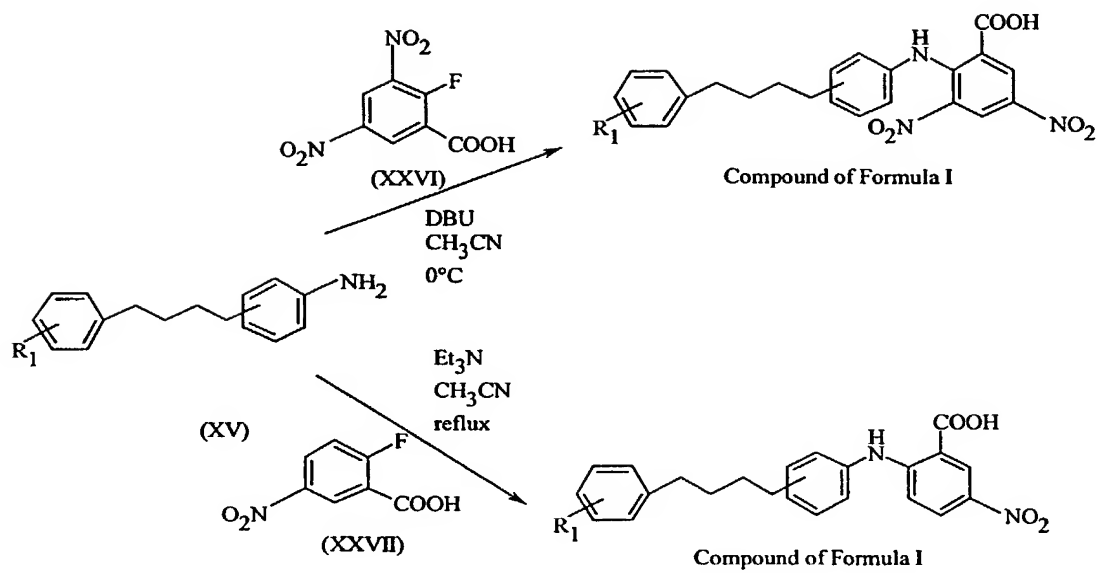
Scheme 7



R is an ester forming group such as alkyl or benzyl.

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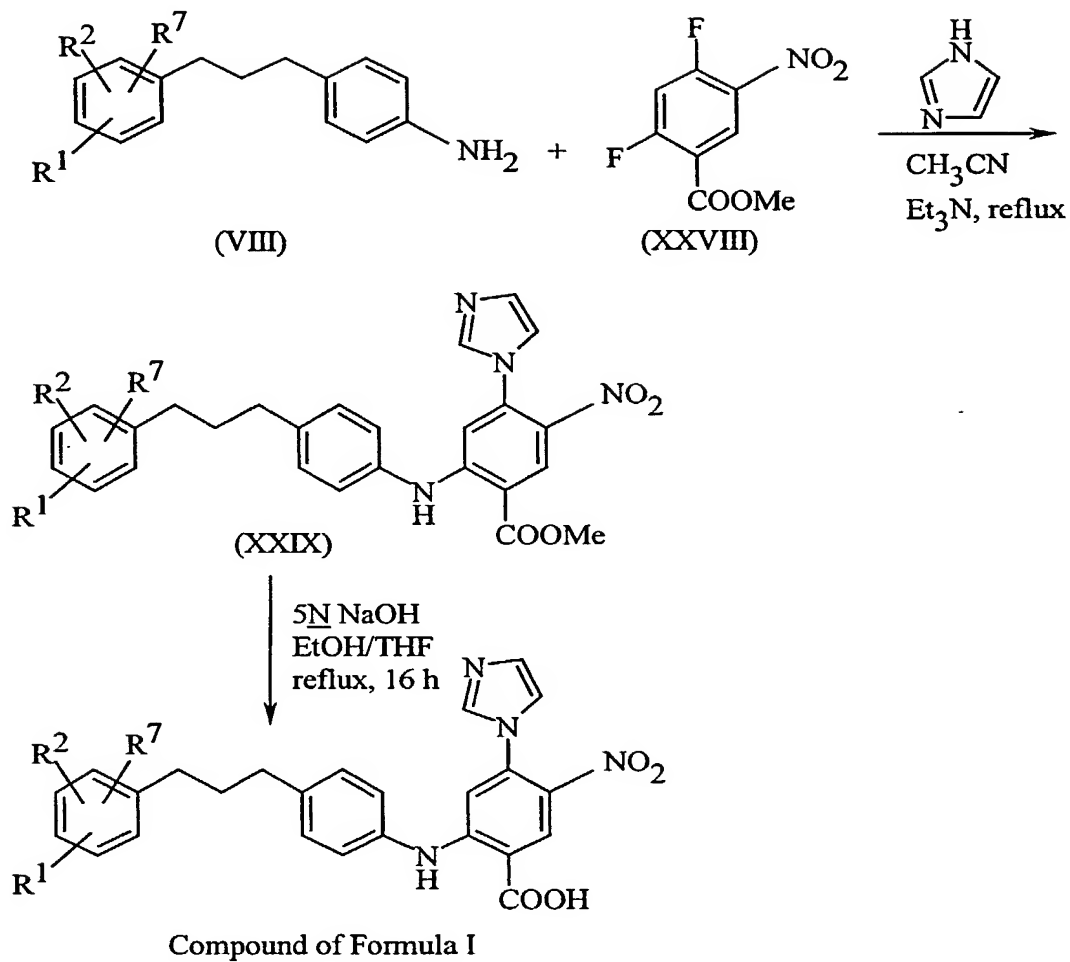
Scheme 8





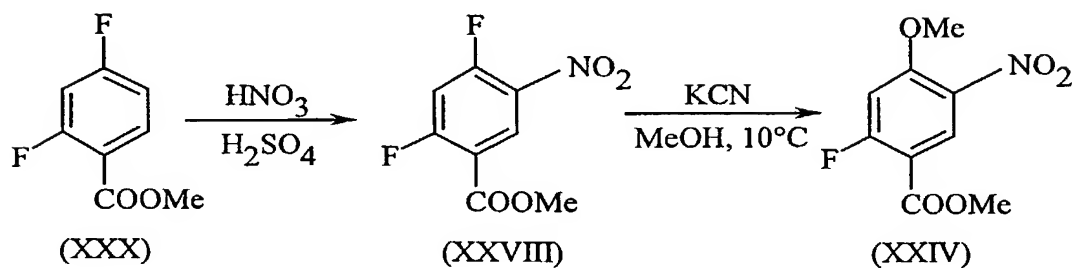
-43-

Scheme 9



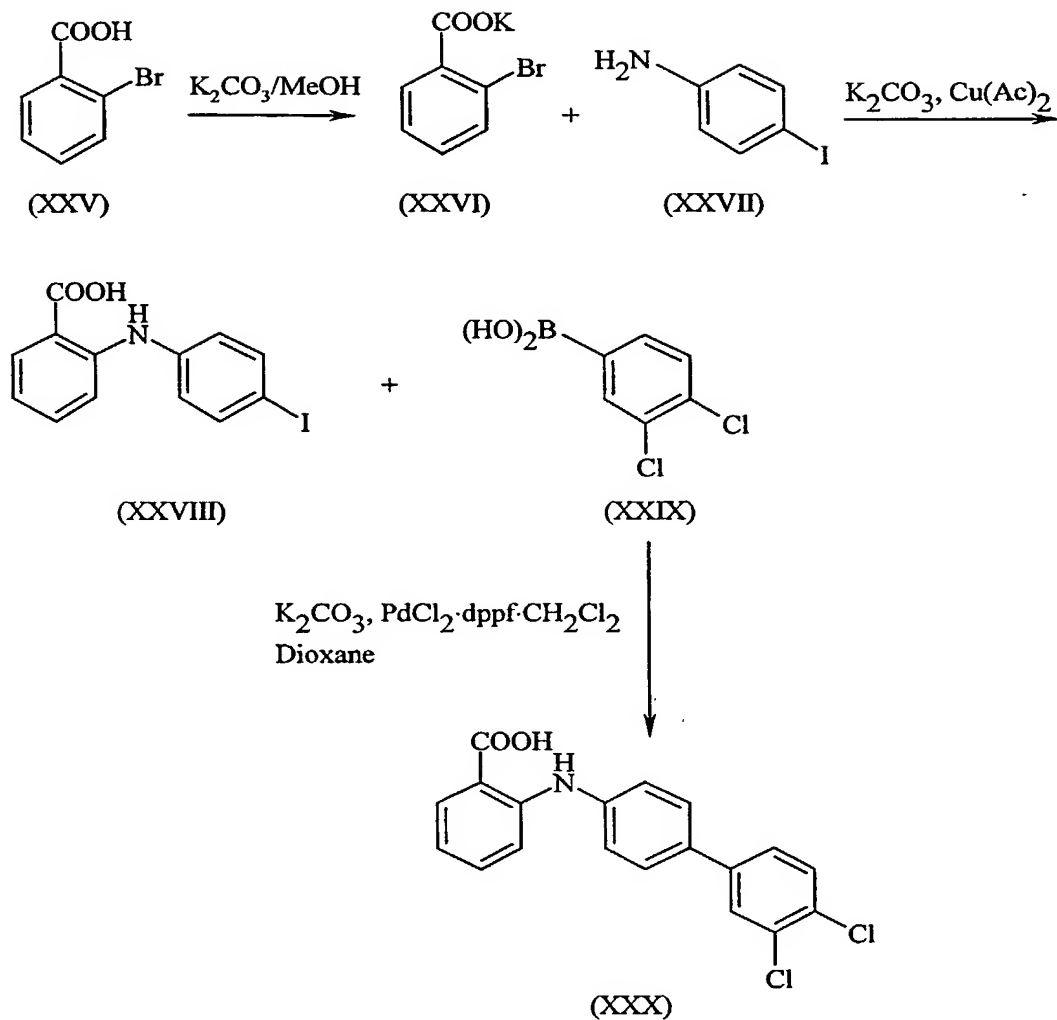
### Synthesis of Fluoro-Intermediate

Scheme 10



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Scheme 11



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## EXAMPLE 1

Preparation of 2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid

Step A (Scheme 1): Preparation of 1,2-Dichloro-4-[2-(4-nitrophenyl)ethenyl]-benzene

5           A mixture of *p*-nitrophenylacetic acid (51.23 g, 0.28 mol) and 3,4-dichlorobenzaldehyde (49.50 g, 0.28 mol) in piperidine (50 mL) was heated to 150-160°C for 5 hours under a N<sub>2</sub> atmosphere. After cooling the reaction mixture, the precipitate was triturated in boiling methanol (MeOH) (50 mL) and then cooled to -5°C for 12 hours. The crystalline precipitate was filtered off, rinsed  
10       with cold MeOH and dried at room temperature in a vacuum oven overnight to yield an orange solid, 22.71 g (0.077 mol, 27%) of the desired product.  
mp 190-191°C.  
MS:294.9 (M<sup>+</sup>).

Step B (Scheme 1): Preparation of 4-[2-(3,4-Dichlorophenyl)ethyl]benzenamine

15           A sample of 1,2-dichloro-4-[2-(4-nitrophenyl)ethenyl]benzene (98.0 g, 0.33 mol) in tetrahydrofuran (THF) (1.6 L) was reduced in the presence of Raney Nickel (Ra-Ni) (20 g) at 25°C to 40°C (ΔP = 13.5 psi) under a hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give an orange solid, 85.0 g (0.32 mol, 95.8%) of the desired product.  
20       mp 68-70°C.  
MS: 266.1 (M<sup>+</sup>).

Step C (Scheme 6): Preparation of  
2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid

Method A

25           A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (28.37 g, 106.59 mmol), methyl 2-bromobenzoate (19.10 g, 88.82 mmol), cesium carbonate (40.52 g, 124.35 mmol), tris(dibenzylideneacetone-dipaladium(0)) (2.44 g, 2.67 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98%, (*S*)-tol-BINAP) (2.71 g, 4.00 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (300 mL)

Found: C, 65.68; H, 4.58; N, 3.60.

# EXAMPLE 2

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester

A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (600 mg, 2.25 mmol), 2-bromo-5-nitrobenzoic acid methyl ester (489 mg, 1.88 mmol), cesium carbonate (857 mg, 2.62 mmol), tris(dibenzylideneacetone-dipaladium(0) (51 mg, 0.056 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl) (98%, (*S*)-tol-BINAP) (58 mg, 0.085 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (16 mL) was heated to 100°C for 12 hours under N<sub>2</sub>. After cooling, the reaction mixture was diluted with ether, filtered through celite and rinsed thoroughly with ether. The filtrate was evaporated to dryness to give a brown residue. Purification by flash chromatography (silica gel, 5% EtOAc/hexane) yielded 540 mg (1.21 mmol, 64%) of the desired product. mp 107-108°C.

Analysis for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>4</sub>: Calcd: C, 59.34; H, 4.07; N, 6.29.

Found: C, 59.03; H, 4.04; N, 5.99.

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

A solution of 2-{4-[2-(3,4-dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (340 mg, 0.76 mmol) and 1N NaOH (aq.) (4.0 mL) in EtOH (4.0 mL) and THF (4.0 mL) was heated to reflux for 16 hours. The solvent was removed in vacuum. The residue was diluted with H<sub>2</sub>O and acidified with concentrated HCl to pH 1. The mixture was then extracted with methylene chloride, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to yield a yellow solid, 329 mg (0.76 mmol, 100%) of the desired product. mp 214-217°C.

Analysis for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>4</sub>: Calcd: C, 58.49; H, 3.74; N, 6.50.

Found: C, 58.24; H, 3.81; N, 6.28.

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### EXAMPLE 3

Preparation of 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

To a cooled (-78°C) solution of 4-[2-(3,4-dichloro-phenyl)-ethyl]phenylamine (0.836 g, 3.14 mmol) in THF (20 mL), LHDMS (6.28 mL, 1 M in THF, 6.28 mmol) was added dropwise. The reaction mixture was allowed to stir at -78°C for 10 minutes. A solution of 2-flouro-4-methoxy-5-nitrobenzoic acid methyl ester (0.72 g, 3.14 mmol) in THF (30 mL) was added dropwise, and this solution was stirred for 30 minutes at -78°C. The reaction mixture was allowed to gradually warm to room temperature and stir for 2 hours under a N<sub>2</sub> atmosphere. The reaction mixture was diluted with ethyl acetate (EtOAc), and acidified with 5N HCl (pH 3). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to yield a brown residue. To a solution of this residue in EtOH (20 mL) and THF (40 mL), 5N NaOH (50 mL) was added, and the mixture was refluxed for overnight. The solvent was removed in vacuum, and the residue was acidified with concentrated HCl (pH 3). The precipitate was collected by filtration, triturated with boiling MeOH-H<sub>2</sub>O (1:1), and dried in a vacuum oven for 16 hours to give Example 3, an orange solid (0.70 g, 1.51 mmol, 48%). mp 208-209°C. Analysis for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>Cl<sub>2</sub>: Calcd: C, 57.28; H, 3.93; N, 6.07. Found: C, 57.43; H, 3.69; N, 5.86.

### EXAMPLE 4

Preparation of 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]-benzene

The title compound was prepared from *p*-nitrophenylacetic acid (25.0 g, 0.14 mol), and 3,4-dimethoxybenzaldehyde (21.0 g, 0.14 mol) in piperidine (5 mL) using the procedure described in Example 1, Step A, to yield a yellow solid, 13.4 g (0.047 mol, 34%) of the desired product. mp: 133-134°C.

Analysis of C<sub>16</sub>H<sub>15</sub>N<sub>1</sub>O<sub>4</sub>: Calcd: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.81; H, 5.27; N, 4.84.

Step B (Scheme 1): Preparation of 4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamine

1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]benzene (12.1 g, 0.042 mol) was reduced in the presence of 10% Pd-C (2.0 g) in dimethylformamide (DMF) (120 mL) at 25°C under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo to give a solid. The solid was recrystallized from MeOH (400 mL) to yield a white crystalline product, 6.8 g (0.026 mol, 63%) of the desired product. mp 115-116°C.

Analysis for  $C_{16}H_{19}N_1O_2$ : Calcd: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.39; N, 5.35.

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamino}benzoic acid

The title compound was prepared from 4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamine (9.25 g, 0.036 mol), 2-chlorobenzoic acid (5.2 g, 0.036 mol), anhydrous potassium carbonate (15.0 g, 0.11 mol), copper powder (0.45 g, 0.007 mol), and a catalytic amount of copper(I) chloride in dry DMF (75 mL) using the procedure described in Example 1, Step C, Method B. After crystallization with MeOH/H<sub>2</sub>O, 4.5 g (0.012 mol, 33%) of the desired product was obtained. mp: 137-139°C.

Analysis for  $C_{23}H_{23}N_1O_4$ : Calcd: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.47; H, 6.03; N, 3.78.

Step D: Preparation of 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid

To a solution of 2-{4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid (0.28 g, 0.74 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), BBr<sub>3</sub> (3.5 mL, 1M in CH<sub>2</sub>Cl<sub>2</sub>, 3.5 mmol) was added at room temperature under a N<sub>2</sub> atmosphere. The reaction mixture was allowed to stir at room temperature for 2 hours and then poured into ice water (50 mL). This mixture was extracted with EtOAc, and the organic layer was washed two times with water, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and

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concentrated in vacuo to yield 0.24 g (0.69 mmol, 93%) of the desired product.  
mp 215-217°C.

Analysis for  $C_{21}H_{19}NO_4$ : Calcd: C, 72.19; H, 5.48; N, 4.00. Found: C, 71.80;  
H, 5.46; N, 3.99.

5

## EXAMPLE 5

Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,1-Dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene

10 The title compound was prepared from *p*-nitrophenylacetic acid (9.92 g, 0.055 mol) and 4-dibutylamino-benzaldehyde (14.32 g, 0.055 mol) in piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a red solid, 4.12 g (0.012 mol, 16%) of the desired product.

MS: 352.2. ( $M^+$ ); 353.2. ( $MH^+$ ).

15 Step B (Scheme 1): Preparation of 4-[2-(4,4-Dibutylaminophenyl)ethyl]-phenylamine

The title compound was prepared from 1,1-dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene (4.10 g, 11.63 mmol) and Ra-Ni (2.0 g) in MeOH (100 mL) at 21°C to 32°C ( $\Delta P = 3.6$  psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a colorless oil,  
20 3.49 g (10.76 mmol, 92.6%) of the desired product.

MS: 325.3 ( $MH^+$ ).

Step C (Scheme 6): Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}-benzoic acid

25 The title compound was prepared from 2-chlorobenzoic acid (1.46 g, 9.36 mmol), 4-[2-(4,4-dibutylaminophenyl)ethyl]phenylamine (3.31 g, 10.20 mmol), anhydrous potassium carbonate (4.27 g, 30.88 mmol), copper powder (1.25 g, 19.65 mmol), and copper(I) chloride (0.092 g, 0.93 mmol) in dry DMF (30 mL) using the procedure described in Example 1, Step C, Method B.



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This procedure yielded a 0.39 g (0.87 mmol, 8.6%) of the desired product.

mp 115-117°C.

Analysis for C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>: Calcd: C, 78.34; H, 8.16; N, 6.30. Found: C, 78.15;

H, 8.07; N, 6.10.

5

## EXAMPLE 6

Preparation of 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,2,3-Trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene

10

The title compound was prepared from *p*-nitrophenylacetic acid (18.6 g, 0.10 mol), 3,4,5-trimethoxy-benzaldehyde (19.6 g, 0.10 mol) and piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a solid, 13.0 g (0.041 mol, 41%) of the desired product. mp: 192-195°C.

Step B (Scheme 1): Preparation of 4-[2-(3,4,5-Trimethoxy-phenyl)ethyl]-phenylamine

15

The title compound was prepared from 1,2,3-trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene (9.5 g, 0.03 mol) and Ra-Ni (1.0 g) in THF (50 mL) at 21-26°C (ΔP = 9.6 psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a tan powder, 6.6 g (0.023 mol, 74%) of the desired product. mp 91-93°C.

20

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid methyl ester

The title compound was prepared from 4-[2-(3,4,5-trimethoxyphenyl)-ethyl]phenylamine (0.75 g, 2.61 mmol), methyl 2-bromobenzoate (0.47 g, 2.17 mmol), cesium carbonate (0.99 g, 3.04 mmol), tris(dibenzylideneacetone-dipaladium(0) (0.06 g, 0.065 mmol) and (*S*)-(-0-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98% (*S*)-Tol-BINAP) (0.066 g, 0.098 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (100 mL) using the procedure described in Example 1, Step C, Method A to yield a yellow oil, 0.69 g (1.63 mmol, 76%) of the desired product.

25

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Analysis for  $C_{25}H_{27}N_1O_5$ : Calcd: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.53; H, 6.24; N, 3.14.

Preparation of 2-{4-[2-(3,4,5-Trimethoxy-phenyl)ethyl]phenylamino}-benzoic acid

- 5 To a solution of 2-{4-[2-(3,4,5-trimethoxyphenyl)ethyl]phenylamino}-benzoic acid methyl ester (0.62 g, 1.47 mmol) in THF-EtOH (2:1, 6 mL), 1N NaOH solution (4 mL) was added, and the reaction mixture was heated to reflux for 5 hours. The reaction mixture was then concentrated in vacuo to remove the organic solvent. The residue was acidified with concentrated HCl (pH 3). This  
10 precipitate was collected by filtration, triturated with boiling MeOH-H<sub>2</sub>O (4:1) and dried in vacuum at room temperature for 16 hours to give the title compound as a white solid, 0.59 g (1.45 mmol, 98.5%). mp 146.0-147.0°C.
- Analysis for  $C_{24}H_{25}N_1O_5$ : Calcd: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.54; H, 6.43; N, 3.15.

- 15 Step D: Preparation of 2-{4-[2-(3,4,5-Trihydroxyphenyl)ethyl]phenylamino}-benzoic acid

- The title compound was prepared from 2-{4-[2-(3,4,5-trimethoxy-phenyl)-ethyl]phenylamino}benzoic acid (0.50 g, 1.23 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and BBr<sub>3</sub> (10 mL, 1M in CH<sub>2</sub>Cl<sub>2</sub>, 10.0 mmol) using the procedure described in  
20 Example 4, Step D. This procedure yielded a green solid, 0.25 g (0.68 mmol, 65%) of the desired product. mp: 160.0-162.0°C.
- Analysis for  $C_{21}H_{19}N_1O_5 \cdot 1.44 H_2O$ : Calcd: C, 64.46; H, 5.64; N, 3.58. Found: C, 64.07; H, 5.27; N, 3.39.

#### EXAMPLE 7

- 25 Preparation of 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

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Step A' (Scheme 2): Preparation of 3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone

Sodium hydroxide (7.3 g, 0.18 mol) was dissolved in water (80 mL) and 95% EtOH (80 mL) and cooled to 10°C with an ice-H<sub>2</sub>O bath.

5 3,4-Dichlorobenzaldehyde (31.8 g, 0.18 mol) was added in one portion. After the addition, the mixture was warmed to 15°C. 1-(4-Nitrophenyl)ethanone (30.0 g, 0.18 mol) was added at this temperature with rigorous stirring. After stirring for 5 minutes, the reaction mixture was diluted with 95% EtOH (300 mL). The resulting tan mixture was stirred at room temperature for 30 minutes, then stirred  
10 with an ice-H<sub>2</sub>O bath underneath the flask for 2 hours. The light brown solid was filtered off, washed with H<sub>2</sub>O, and air-dried. The solid was dissolved in hot THF (1.5 L) and treated with charcoal. The resulting mixture was filtered off, and the filtrate was diluted with 95% EtOH (500 mL). This solution was filtered and oven-dried (40°C) to yield a light brown solid, 38.56 g (0.12 mol, 66%) of the title  
15 compound. mp 220-223°C.

Analysis for C<sub>15</sub>H<sub>9</sub>Cl<sub>2</sub>NO<sub>3</sub>: Calcd: C, 55.93; H, 2.82; Cl, 22.01; N, 4.35.

Found: C, 55.79; H, 2.93; Cl, 22.16; N, 4.32.

Step B' (Scheme 2): Preparation of 1-(4-Amino-phenyl)-3-(3,4-dichlorophenyl)propan-1-one

20 3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone (34.56 g, 0.11 mol) was reduced in the presence of Ra-Ni (3.0 g) in THF (250 mL) at 20°C to 32°C (ΔP = 33.4 psi) under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo and recrystallized from MeOH (100 mL) to give a light yellow solid, 23.5 g (0.080 mol, 75%) of the desired product. mp 127-129°C.

25 Analysis for C<sub>15</sub>H<sub>13</sub>Cl<sub>2</sub>NO: Calcd: C, 61.24; H, 4.45; N, 4.76; Cl, 24.10.

Found: C, 60.91; H, 4.60; N, 4.70; Cl, 23.98.

Step C' (Scheme 2): Preparation of 4-[3-(3,4-Dichlorophenyl)propyl]phenylamine

A mixture of 1-(4-aminophenyl)-3-(3,4-dichlorophenyl)propan-1-one (20.0 g, 0.068 mol), NH<sub>2</sub>NH<sub>2</sub>-H<sub>2</sub>O (16 mL), and KOH (85%, 5.6 g) in ethylene

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glycol (160 mL) was heated to reflux under a N<sub>2</sub> atmosphere for 16 hours. After cooling to room temperature, the reaction mixture was poured into ice-H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 L). The layers were separated, and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford an oil. Purification by  
5 flash chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>) yielded an oil, 14.00 g (0.05 mol, 73%) of the desired product.

Analysis for C<sub>15</sub>H<sub>15</sub>Cl<sub>2</sub>N: Calcd: C, 64.30; H, 5.40; N, 4.99; Cl, 25.31.

Found: C, 64.21; H, 5.59; N, 5.24; Cl, 24.87.

#### Preparation of 2,4-Difluoro-5-nitrobenzoic acid methyl ester

10 Fuming nitric acid 90% (8.5 mL, 0.19 mol) was added with gentle stirring to concentrated sulfuric acid 98% (125 mL) in a 1 L beaker. After stirring for 10 minutes at room temperature, 2,4-difluorobenzoic acid methyl ester (21.9 g, 0.127 mol) was added dropwise. After the addition, the reaction mixture was allowed to stir gently for 40 minutes at room temperature. The reaction mixture  
15 was then poured into ice-H<sub>2</sub>O (1 L) and stirred for 10 minutes. The mixture was extracted with EtOAc. The layers were separated, and the organic layer was washed sequentially with 1N NaCl, saturated NaHCO<sub>3</sub>, H<sub>2</sub>O and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to afford a yellow residue. This residue was washed with 10% EtOAc/hexane, filtered, and dried to yield a pale  
20 yellow solid, 29.0 g (0.133 mol, 82%). mp 78-80°C.

Analysis for C<sub>8</sub>H<sub>5</sub>F<sub>2</sub>NO<sub>4</sub>: Calcd: C, 44.25; H, 2.32; N, 6.45. Found: C, 44.18; H, 2.39; N, 6.14.

#### Preparation of 2-Fluoro-4-methoxy-5-nitrobenzoic acid methyl ester

25 A mixture of sodium metal (1.27 g, 0.055 mol) and MeOH (250 mL) was stirred at 0°C for 10 minutes. This solution was added to a solution of 2-fluoro-5-nitrobenzoic acid methyl ester (10.0 g, 0.046 mol) in MeOH (250 mL), and the mixture was stirred for 20 minutes at 0°C to 5°C. The reaction mixture was then allowed to warm to room temperature and stir for 2 hours. The mixture was then filtered to give an off-white precipitate. Recrystallization with CHCl<sub>3</sub> (70 mL)

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yielded an off-white crystalline solid, 1.825 g (0.008 mol, 17%) of the title compound.

Analysis for  $C_9H_8F_1N_1O_5$ : Calcd: C, 47.17; H, 3.52; N, 6.11. Found: C, 47.09; H, 3.47; N, 6.00.

5 Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

A mixture of 4-[3-(3,4-dichloro-phenyl)propyl]phenylamine (0.94 g, 3.3 mmol), 2-fluoro-4-methoxy-5-nitro-benzoic acid methyl ester (0.75 g, 3.3 mmol), and  $Et_3N$  (0.46 mL) in  $CH_3CN$  (30 mL) was heated to reflux for 10 120 hours. The reaction mixture was cooled to room temperature, diluted with  $CH_2Cl_2$  and washed with saturated  $NaHCO_3$ . The organic layer was dried ( $Na_2SO_4$ ) and concentrated to give a solid. Recrystallization with MeOH yielded 0.67 g (1.37 mmol, 42%) of the desired product.

Analysis for  $C_{24}H_{22}N_2Cl_2O_5 \cdot 0.42H_2O$ : Calcd: C, 58.01; H, 4.63. N, 5.64; 15 Found: C, 57.61; H, 4.51; N, 5.94.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

To a solution of 2-{4-[3-(3,4-dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (0.30 g, 0.061 mol) in THF (5 mL), 20 1N NaOH (aq.) (2.5 mL) was added, and the mixture was stirred for 36 hours at room temperature. The solvent was removed, and the residue was acidified with concentrated HCl to pH 3. The precipitate was collected by filtration and dried in vacuum for 16 hours. Recrystallization with MeOH gave the title compound as an orange solid 0.21 g (0.043 mol, 70%). mp 200-201°C.

25 Analysis for  $C_{23}H_{20}N_2O_5Cl_2 \cdot 0.2H_2O$ : Calcd: C, 57.68; H, 4.29; N, 5.85; Cl, 14.81. Found: C, 57.71; H, 4.34; N, 5.58; Cl, 14.56.

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EXAMPLE 8

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino]-4-imidazo-1-yl-5-nitrobenzoic acid

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino]-4-imidazo-1-yl-5-nitrobenzoic acid methyl ester

A mixture of 2,4-difluoro-5-nitrobenzoic acid methyl ester (1.63 g, 7.5 mmol), imidazole (0.56 g, 8.25 mmol), and Et<sub>3</sub>N (1.14 mL, 8.25 mmol) in CH<sub>3</sub>CN (50 mL) was stirred for 16 hours at room temperature. To this deep orange solution, 4-[3-(3,4-dichlorophenyl)propyl]phenylamine (2.10 g, 7.5 mmol) and triethylamine (Et<sub>3</sub>N) (1.14 mL, 8.25 mmol) was added, and the mixture was heated to reflux for overnight. The reaction mixture was cooled and concentrated in vacuo to afford a residue. This residue was diluted with CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated K<sub>2</sub>HCO<sub>3</sub> solution. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to give a crude oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 1.0 g (1.90 mmol, 25%) of the desired product.

MS: 524.1 (M<sup>+</sup>).

Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino]-4-imidazo-1-1-yl-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[2-[-(3,4-dichlorophenyl)propyl]phenylamino]-4-imidazo-1-yl-5-nitrobenzoic acid methyl ester (1.0 g, 1.9 mmol), 1N NaOH (2.0 mL) in THF (30 mL) using the procedure described in Example 8. This procedure yielded an orange solid, 0.30 g (0.6 mmol, 32%) of the desired product.

Analysis for C<sub>25</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>·0.2H<sub>2</sub>O: Calcd: C, 58.31; H, 3.99; N, 10.88; Cl, 13.89. Found: C, 58.34; H, 4.07; N, 10.73; Cl, 13.41.

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## EXAMPLE 9

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}-benzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid methyl ester

5           The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]-phenylamine (600 mg, 2.14 mmol), 2-bromobenzoic acid methyl ester (380 mg, 1.78 mmol), cesium carbonate (812 mg, 2.49 mmol), tris(dibenzylideneacetone-dipaladium(0) (49 mg, 0.053 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98%, (*S*)-tol-BINAP) (54 mg, 0.080 mmol) (Ligand/Pd = 1.5) in  
10           anhydrous toluene (15 mL) using the procedure described in Example 2, Step C. This procedure yielded an yellow oil, 0.61 g (1.47 mmol, 69%) of the desired product.

MS: 414 ( $M^+$ ), 416 ( $MH^+$ ).

Analysis for  $C_{23}H_{21}Cl_2O_2N \cdot 0.4 H_2O$ : Calcd: C, 65.25; H, 5.23; N, 3.30.

15           Found: C, 65.76; H, 5.18; N, 3.10.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

          The title compound was prepared from 2-{4-[3-(3,4-dichlorophenyl)-propyl]phenylamino}benzoic acid methyl ester (0.41 g, 0.99 mmol), 1*N* NaOH (4.0 mL) in EtOH (4 mL) and THF (4 mL) using the procedure described in  
20           Example 2. This procedure yielded a yellow solid, 0.32 g (0.80 mmol, 81%) of the desired product. mp 120-126°C.

Analysis for  $C_{22}H_{19}Cl_2O_2N_1 \cdot 0.75 H_2O$ : Calcd: C, 64.04; H, 5.00; N, 3.39.

Found: C, 64.17; H, 4.69; N, 3.18.

## EXAMPLE 10

25           Preparation of 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid

Preparation of (*trans*)-3-(3,4-Dichlorophenyl)-2-propenal

          A mixture of 3,4-dichlorobenzaldehyde (140.0 g, 0.8 mol) and acetaldehyde (300 mL) was cooled to 5°C. Potassium hydroxide (5.1 g, 0.091 mol) was dissolved in hot MeOH (40 mL), and the resulting solution was





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by flash chromatography (silica gel, 20% EtOAc/hexane) yielded 16.0 g (0.05 mol, 28%) of the desired product. mp 125-135°C.

Analysis for  $C_{16}H_{11}Cl_2NO_2$ : Calcd: C, 60.02; H, 3.46; N, 4.37, Cl, 22.15.

Found: C, 59.77; H, 3.47; N, 4.40; Cl, 22.39.

# 5 Preparation of 4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamine

The title compound was prepared from (*trans*), (*trans*)-1,2-dichloro-4-[4-(4-nitrophenyl)-1,3-butadienyl]benzene (15.42 g, 0.048 mol), Ra-Ni (1 g) at 20°C to 26°C ( $\Delta P = 19.3$  psi) under a hydrogen atmosphere in THF (75 mL) and MeOH (75 mL) using the procedure described in Example 1, Step B. This procedure yield a solid, 10.97 g (0.037 mol, 78%) of the desired product. mp 50-52°C.

Analysis of  $C_{16}H_{17}N_1Cl_2$ : Calcd: C, 65.32; H, 5.82; N, 4.76. Found: C, 65.43; H, 5.84; N, 4.61.

# 15 Preparation of 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid

The title compound, mp 98-105°C, was prepared from 4-[4-(3,4-dichlorophenyl)butyl]phenylamine (0.50 g, 1.7 mmol), 2-chlorobenzoic acid (0.24 g, 1.56 mmol), anhydrous potassium carbonate (0.71 g, 5.15 mmol), copper powder (0.21 g, 3.28 mmol), and copper(I) chloride (0.015 g, 0.15 mmol) in dry DMF (5 mL) using the procedure described in Example 1, Step C, Method B.

## 20 EXAMPLE 11

### Preparation of 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid

A mixture of 2-fluoro-5-nitrobenzoic acid (1.85 g, 0.01 mol), 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (2.94 g, 0.01 mol) and  $Et_3N$  (2.80 mL) in acetonitrile (110 mL) was heated to reflux for 48 hours. The reaction mixture was cooled and concentrated in vacuo to remove the solvent. The residue was dissolved in  $CH_2Cl_2$  and washed with diluted HCl. The organic layer was dried ( $Na_2SO_4$ ), concentrated in vacuo to give a crude solid. Purification by flash

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chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>) yielded 1.40 g (0.003 mol, 30%) of the desired product.

Analysis for C<sub>23</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>Cl<sub>2</sub>: Calcd: C, 60.27; H, 4.18; N, 6.11; Cl, 14.47.

Found: C, 60.16; H, 4.41; N, 6.09; Cl, 15.69.

5

## EXAMPLE 12

Preparation of 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid

To a cooled (0°C) solution of 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (1.47 g, 5.0 mmol) and DBU (0.75 mL, 7.5 mmol) in acetonitrile (25 mL), a solution of 2-fluoro-2,5-dinitrobenzoic acid (1.15 g, 5.0 mmol) in acetonitrile (15 mL) was added dropwise. After stirring for 30 minutes at 0°C, the reaction mixture was neutralized with dilute HCl and extracted with EtOAc, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to afford a crude residue.

Recrystallization with EtOH yielded a bright orange solid, 2.06 g (4.1 mmol, 82%) of the title compound.

Analysis for C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>6</sub>: Calcd: C, 54.77; H, 3.80; N, 8.33; Cl, 14.06.

Found: C, 54.68; H, 4.00; N, 8.12; Cl, 13.81.

## EXAMPLE 13

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid

Preparation of Bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane

A mixture of 4-bromomethyl-1,2-dichlorobenzene (2.40 g, 0.01 mol), and triphenylphosphine (5.24 g, 0.02 mol) in toluene (30 mL) was stirred for 16 hours at room temperature. The solid was filtered, rinsed with toluene, and oven-dried at room temperature to yield a white powder, 3.95 g (0.0078 mol, 78%) of the desired product.

<sup>1</sup>H NMR [dimethylsulfoxide (DMSO):ppm] :7.89-7.61 (m, 15H), 7.50 (d, J=8.3 Hz, 1H), 7.04 (t, J=2.3 Hz, 1H), 6.97 (m, 1H), 5.20 (d, J=15.9 Hz, 2H).

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Preparation of 4-(4-Nitrophenyl)butyraldehyde

To a cooled solution (-70°C) of oxalyl chloride (2.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 14.1 mL, 28.2 mmol), dimethylsulfoxide (DMSO) (4.40 g, 56.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added dropwise. The resulting reaction mixture was then stirred for 30 minutes at -70°C under a nitrogen atmosphere. A solution of 4-(4-nitrophenyl)butan-1-ol (5.00 g, 25.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added dropwise, and the reaction mixture was stirred for 1 hour at -70°C. Et<sub>3</sub>N (16 mL, 115 mmol) was added, and the reaction mixture was then allowed to gradually warm to room temperature and stir for 30 minutes. The mixture was then quenched with H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 50% EtOAc/hexane) yielded 3.20 g (16.56 mmol, 65%) of the desired product.

<sup>1</sup>H NMR (DMSO:ppm): 9.75 (s, 1H), 8.12 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 2.72 (t, *J*=7.7 Hz, 2H), 2.47 (t, *J*=7.1 Hz, 2H), 1.94 (m, 2H).

Preparation of 1,2-Dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene

A solution of bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane (3.95 g, 7.9 mmol) in dry THF (20 mL) was cooled to 0°C. LHDMS (1.0 M/THF, 9 mL, 9.0 mol) was added dropwise to maintain the temperature at 0°C. After stirring for 30 minutes, a solution of 4-(4-nitro-phenyl)butyraldehyde (1.45 g, 7.5 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to room temperature within 2 hours. The mixture was then quenched with H<sub>2</sub>O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H<sub>2</sub>O, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 2.5 g (7.4 mmol, 99%) of the desired product. MS: 335 (M<sup>+</sup>), 337 (MH<sup>+</sup>).

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## Preparation of 4-[5-(3,4-Dichlorophenyl)pentyl]phenylamine

The title compound was prepared from 1,2-dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene (2.5 g, 7.4 mmol), Ra-Ni (1 g) in THF (50 mL) at 25°C to 40°C ( $\Delta P = 9.9$  psi) using the procedure described in Example 1, Step B. This procedure yielded 1.06 g (3.4 mmol, 46%) of the desired product.

$^1\text{H}$  NMR (DMSO:ppm): 7.45 (d,  $J=8.3$  Hz, 1H), 7.41 (d,  $J=2.2$  Hz, 1H), 7.12 (m, 1H), 6.74 (d,  $J=8.3$  Hz, 2H), 6.40 (d,  $J=8.3$  Hz, 2H), 4.73 (s, 2H), 2.50 (t,  $J=7.7$  Hz, 2H), 2.31 (t,  $J=7.6$  Hz, 2H), 1.6-1.5 (m, 4H), 1.5-1.4 (m, 2H).

## Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-5-nitrobenzoic acid

To a cooled (-78°C) solution of 4-[5-(3,4-dichlorophenyl)pentyl]phenylamine (0.231 g, 0.75 mmol) in THF (2 mL), LHDMS (2.25 mL, 1 M in hexane, 2.25 mmol) was added dropwise. The reaction mixture was allowed to stir at -78°C for 10 minutes. A solution of 2-fluoro-5-nitrobenzoic acid (0.139 g, 0.75 mmol) in THF (2 mL) was added dropwise, and this solution was stirred for 30 minutes at -78°C. The reaction mixture was allowed to gradually warm to room temperature and stir for 2 hours under  $\text{N}_2$  atmosphere. The reaction mixture was diluted with EtOAc, and acidified with 1N HCl (pH 3). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo to yield a brown residue.

Purification by flash chromatography (silica gel, 2% MeOH/ $\text{CH}_2\text{Cl}_2$ ) then recrystallization with MeOH yielded 265 mg (0.56 mmol, 75%) of the desired product. mp 147-148°C.

Analysis for  $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4 \cdot 0.37\text{H}_2\text{O}$ : Calcd: C, 60.05; H, 4.77; N, 5.84.

Found: C, 59.67; H, 4.64; N, 5.51.

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## EXAMPLE 14

Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[5-(3,4-dichlorophenyl)pentyl]phenylamine (231 mg, 0.75 mmol), LHDMS (6.28 mL, 1 M in THF, 6.28 mmol) and 2-fluoro-4-methoxy-5-nitrobenzoic acid methyl ester (172 g, 0.75 mmol) in THF (5 mL) using the procedure described in Example 13.

Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 145 mg (0.28 mmol, 37%) of the desired product.

MS: 515.2 ( $M^+$ ), 517.2 ( $MH^+$ ).

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[5-(3,4-dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (145 mg, 0.28 mmol) and 1N NaOH (aq.) (0.56 mL) in THF (1.2 mL) using the procedure described in Example 2. Purification by flash chromatography (silica gel, 10% MeOH/ $CH_2Cl_2$ ), then recrystallization with MeOH yielded 58 mg (0.12 mmol, 41%) of the desired product. mp 192-193°C.

Analysis for  $C_{25}H_{24}Cl_2N_2O_5$ : Calcd: C, 59.65; H, 4.81; N, 5.56.

Found: C, 59.29; H, 4.58; N, 5.36.

## EXAMPLE 15

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]phenylamine (420 mg, 1.50 mmol), 2-bromobenzoic acid methyl ester (310 mg,



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Analysis for  $C_{24}H_{24}O_4N_2 \cdot 0.25 H_2O$ : Calcd: C, 71.27; H, 5.98; N, 6.93.

Found: C, 70.48; H, 6.03; N, 6.85.

Preparation of 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

5           The title compound was prepared 2-{4-[2-(3,4-dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (1.12 g, 2.76 mmol), 1N NaOH (50 mL) in EtOH (50 mL) and THF (50 mL) using the procedure described in Example 2. This procedure yielded a yellow solid, 1.03 g (2.63 mmol, 81%) of the desired product. mp 214-216°C.

10          Analysis for  $C_{23}H_{22}O_4N_2 \cdot 0.25 H_2O$ : Calcd: C, 69.99; H, 5.74; N, 7.18.  
Found: C, 69.90; H, 5.82; N, 6.81.

#### EXAMPLE 17

Preparation of 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino]-benzoic acid

15          Step A (Scheme 1): Preparation of *trans*-1-Chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene

          A mixture of p-nitrophenylacetic acid (51.85 g, 0.29 mol) and 4-chloro-3-trifluoromethylbenzaldehyde (47.85 g, 0.23 mol) in piperidine (19.5 g, 0.23 mol) was heated under  $N_2$  atmosphere to 150°C to 160°C for 1 hour. The reaction  
20          mixture was cooled to 80°C to 100°C and refluxing *i*-PrOH (150 mL) was added. The mixture was continued to cool to room temperature and then placed under refrigeration for 5 hours. The crystalline precipitate was filtered off, rinsed with cold *i*-PrOH, and dried at room temperature in a vacuum oven overnight to yield  
25          *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene as an orange solid, 22.53 g (68.75 mmol, 30%). mp 173-174°C.

MS: 327.0 ( $M^+$ )

Step B (Scheme 1): Preparation of 4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]-benzenamine

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The title compound was prepared from *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene (22.53 g, 0.069 mol) and Ra-Ni (22 g) in THF (0.5 L) at 18°C to 29°C ( $\Delta P = 20.5$  psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a white solid, 20.0 g (66.73 mmol, 97%) of the desired product. mp 62-64°C.

MS: 298.1 ( $M^+$ )

Preparation of 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]-aminobenzoic acid

To a cold solution of 4-[2-(4-chloro-3-trifluoromethylphenyl)ethyl]-benzenamine (4.33 g, 14.45 mmol) in THF (50 mL) at -78°C, was added LHMDS (43.35 mL, 43.35 mmol) (1M/THF) dropwise. Allowed the reaction mixture to stir for 10 minutes at -78°C. A solution of 2-fluorobenzoic acid (2.02 g, 14.45 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 2 hours at -78°C, then warmed to room temperature and let stir for additional 3 hours. The reaction mixture was concentrated *in vacuo* (40°C) to remove the organic solvent. This residue was acidified to pH 3 with 3N HCl (aq.). This precipitate was collected by filtration, rinsed with 10% HCl (40 mL), and dried in vacuum for overnight to give as a pale solid, 4.3 g (10.24 mmol, 70%) of the desired product. mp 150-152°C.

Analysis for  $C_{22}H_{17}O_2N_1ClF_3 \cdot 0.59 H_2O$ : Calcd: C, 61.39; H, 4.26; N, 3.25. Found: C, 61.01; H, 4.34; N, 3.30.

### EXAMPLE 18

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

Preparation of o-Bromobenzoic acid potassium salt

To a solution of o-bromobenzoic acid (201.03 g, 1.0 mol) in MeOH (500 mL),  $K_2CO_3$  (69 g, 1.0 mol) was added. The mixture was concentrated to give the desired product (239.1 g, 1.0 mol, 100%).



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Preparation of 2-[(4-Iodophenyl)amino] benzoic acid

A mixture of o-bromobenzoic acid potassium salt (47.8 g, 0.2 mol), 4-iodoaniline (43.8 g, 0.2 mol),  $K_2CO_3$  (13.8 g, 0.1 mol), and cupric acetate (2.87 g, 6%) in diglyme (100 mL) was heated to reflux for 30 minutes. The reaction mixture was diluted with  $H_2O$  (1.0 L) and filtered. The filtrate was acidified with diluted AcOH. The resulting precipitate was collected by filtration, washed with  $H_2O$  and dried in a vacuum at  $50^\circ C$  for 16 hours. Recrystallization from EtOAc gave the desired product, a solid (29.7 g, 0.087 mol, 44%). mp  $205-206^\circ C$ .

Analysis for  $C_{13}H_{10}N_1O_2I$ : Calcd: C, 45.05; H, 2.97; N, 4.13. Found: C, 45.05; H, 2.97; N, 3.92.

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

A mixture of 3,4-dichlorophenylboronic acid (880 mg, 2.3 mmol), 2-[(4-iodophenyl)amino]benzoic acid (339 mg, 1 mmol),  $PdCl_2 \cdot dppf \cdot CH_2Cl_2$  [1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride, complexed with dichloromethane (1:1)] (67 mg, 0.082 mmol),  $K_2CO_3$  (829 mg, 6 mmol), and  $H_2O$  (2 mL) in dioxane (15 mL) was heated to reflux for 1 hour. The reaction mixture was diluted with EtOAc and filtered. The filtrate was treated with 1N HCl, washed with  $H_2O$ , brine, dried ( $Na_2SO_4$ ), and concentrated in vacuum to give a yellow solid. Purification by flash chromatography (silica gel, 10% MeOH/ $CH_2Cl_2$ ) yielded 272 mg (0.76 mmol, 76%) of the desired product. mp  $>220^\circ C$ .

Analysis for  $C_{19}H_{13}O_2N_1Cl_2$ : Calcd: C, 63.23; H, 3.71; N, 3.88.

Found: C, 62.95; H, 3.73; N, 3.63.

By following the general procedures described above, the following additional invention compounds were prepared:

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## EXAMPLE 19

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

MS: 403 ( $M^+$ ).Analysis for  $C_{26}H_{30}N_2O_2 \cdot 0.40 \text{ mol H}_2\text{O}$ : Calcd: C, 69.31; H, 6.87; N, 6.12.

5 Found: C, 69.29; H, 7.04; N, 6.35.

## EXAMPLE 20

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 150-153°C.

MS: 376 ( $M^+$ ).

## EXAMPLE 21

10 2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 164-167°C.

MS: 376 ( $M^+$ ).Analysis for  $C_{22}H_{20}N_2O_4 \cdot 2.20 \text{ mol H}_2\text{O}$ : Calcd: C, 63.51; H, 5.91; N, 6.73.

Found: C, 63.56; H, 5.45; N, 6.46.

## EXAMPLE 22

15 2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid. mp 110-112°C.

MS: 347 ( $M^{+1+}$ ).

## EXAMPLE 23

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid. mp 109°C.

MS: 333 ( $M^{+1+}$ ).

20

## EXAMPLE 24

2-{4-[2-(4-Aminophenyl)phenylamino]benzoic acid. mp 198-201°C.

MS: 333 ( $M^{+1+}$ ).Analysis for  $C_{21}H_{20}N_2O_2 \cdot 0.1 \text{ mol H}_2\text{O}$ : Calcd: C, 75.47; H, 6.09; N, 8.38.

Found: C, 75.32; H, 6.12; N, 8.27. Found: C, 75.32; H 6.12; N, 8.27.

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EXAMPLE 25

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride. mp 176-177°C

MS: 417 ( $M^{+1+}$ ).

5 Analysis for  $C_{27}H_{32}N_2O_2$ : Calcd: C, 71.59; H, 7.34; N, 6.18; Cl, 7.83. Found: C, 71.31; H, 7.24; N, 6.19; Cl, 7.74.

EXAMPLE 26

2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride monohydrate

10 MS: 389 ( $M^{+1+}$ ).

Analysis for  $C_{25}H_{28}N_2O_2 \cdot HCl \cdot H_2O$ : Calcd: C, 67.78; H, 7.05; N, 6.32; Cl, 8.00.  
Found: C, 67.83; H, 7.01; N, 6.30; Cl, 7.75.

EXAMPLE 27

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino}benzoic acid

15 MS: 431 ( $M^{+1+}$ ).

Analysis for  $C_{28}H_{34}N_2O_2 \cdot 0.2 H_2O$ : Calcd: C, 77.46; H, 7.99; N, 6.45.  
Found: C, 77.43; H, 7.86; N, 6.40.

EXAMPLE 28

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino}benzoic acid.

20 mp 115-117°C.

MS: 374 ( $M^{+}$ ), 375 ( $M^{+1+}$ ).

Analysis for  $C_{24}H_{26}N_2O_2 \cdot 0.1 H_2O$ : Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.57; H, 7.21; N, 7.47.

EXAMPLE 29

25 2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid. mp 133°C.

MS: 375 ( $M^{+1+}$ ).

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Analysis for  $C_{24}H_{26}N_2O_2 \cdot 0.1 H_2O$ : Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.62; H, 7.06; N, 7.36.

#### EXAMPLE 30

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid

5 MS: 431 ( $M^{+1+}$ ).

Analysis for  $C_{28}H_{34}N_2O_2$ : Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.02; H, 8.17; N, 6.50.

#### EXAMPLE 31

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid.

10 mp 95.5-97.5°C.

Analysis for  $C_{35}H_{32}N_2O_2$ : Calcd: C, 82.00; H, 6.29; N, 5.46. Found: C, 81.81; H, 6.58; N, 5.44.

#### EXAMPLE 32

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid

15 MS: 403 ( $M^{+1+}$ ).

Analysis for  $C_{26}H_{30}N_2O_2 \cdot 0.1 H_2O$ : Calcd: C, 77.23; H, 7.53; N, 6.93. Found: C, 77.14; H, 7.82; N, 6.88.

#### EXAMPLE 33

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid. mp 182-184°C.

20 MS: 333 ( $M^{+1+}$ ).

Analysis for  $C_{21}H_{20}N_2O_2 \cdot 0.25 H_2O$ : Calcd: C, 74.87; H, 6.13; N, 8.43. Found: C, 74.86; H, 6.16; N, 8.32.

#### EXAMPLE 34

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid

25 MS: 375 ( $M^{+1+}$ ).

Analysis for  $C_{24}H_{26}N_2O_2 \cdot 0.1 H_2O$ : Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.52; H, 7.22; N, 7.49.

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EXAMPLE 35

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 224°C.

MS: 375 ( $M^{+1+}$ ).

EXAMPLE 36

5 2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 213-215°C.

MS: 375 ( $M^{+1+}$ ).

EXAMPLE 37

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride. mp 189-193°C.

10 MS: 417 ( $M^{+1+}$ ).

Analysis for  $C_{27}H_{32}N_2O_2 \cdot HCl$ : Calcd: C, 71.58; H, 7.34; N, 6.18; Cl, 7.83.

Found: C, 71.48; H, 7.35; N, 6.10; Cl, 7.66.

EXAMPLE 38

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride. mp 175-180°C.

15

MS: 445 ( $M^{+}$ ).

Analysis for  $C_{29}H_{36}N_2O_2 \cdot HCl$ : Calcd: C, 72.40; H, 7.75; N, 5.82; Cl, 7.37.

Found: C, 72.61; H, 7.95; N, 5.78; Cl, 7.23.

EXAMPLE 39

20 2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 176-178°C.

MS: 389 ( $M^{+1+}$ ).

EXAMPLE 40

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 140-145°C.

MS: 389 ( $M^{+1+}$ ).

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## EXAMPLE 41

2-{4-[2-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride. mp 166-171°C.

MS: 389 ( $M^{+1+}$ ).

- 5     Analysis for  $C_{25}H_{28}N_2O_2 \cdot HCl$ : Calcd: C, 70.66; H, 6.88; N, 6.59; Cl, 8.34.  
Found: C, 70.48; H, 6.89; N, 6.57; Cl, 18.39.

## EXAMPLE 42

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid  
monohydrochloride. mp 187-193°C.

- 10     MS: 401 ( $M^{+1+}$ ).

Analysis for  $C_{26}H_{28}N_2O_2 \cdot HCl$ : Calcd: C, 71.46; H, 6.69; N, 6.41; Cl, 8.11.  
Found: C, 71.28; H, 6.73; N, 6.35; Cl, 8.30.

## EXAMPLE 43

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid

- 15     MS: 431 ( $M^{+1+}$ ).

Analysis for  $C_{28}H_{34}N_2O_2$ : Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.91;  
H, 8.03; N, 6.43.

## EXAMPLE 44

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

- 20     MS: 459 ( $M^{+1+}$ ).

Analysis for  $C_{30}H_{38}N_2O_2$ : Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40;  
H, 8.50; N, 6.19.

## EXAMPLE 45

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

- 25     MS: 459 ( $M^{+1+}$ ).

Analysis for  $C_{30}H_{38}N_2O_2$ : Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40;  
H, 8.43; N, 6.11.

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## EXAMPLE 46

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid.

mp 131-136°C.

MS: 397 ( $M^{+1+}$ ).

5 Analysis for  $C_{26}H_{24}N_2O_2 \cdot 0.2 H_2O$ : Calcd: C, 78.05; H, 6.15; N, 7.00. Found: C, 77.95; H, 6.17; N, 7.08.

## EXAMPLE 47

2-{4-[3-(4-Piperidin-1-yl)phenyl]propyl}phenylamino}benzoic acid

MS: 415 ( $M^{+1+}$ ).

10 Analysis for  $C_{27}H_{30}N_2O_2 \cdot 0.2 H_2O$ : Calcd: C, 77.55; H, 7.33; N, 6.70. Found: C, 77.37; H, 7.35; N, 6.63.

## EXAMPLE 48

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid.

mp 57-62°C.

15 MS: 431 ( $M^{+1+}$ ).

Analysis for  $C_{27}H_{30}N_2O_3 \cdot 0.3 H_2O$ : Calcd: C, 74.39; H, 7.07; N, 6.43. Found: C, 74.23; H, 6.97; N, 6.27.

## EXAMPLE 49

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid. mp 236-239°C.

20 MS: 375 ( $M^{+}$ ).

## EXAMPLE 50

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid.

mp 137°C.

MS: 417 ( $M^{+1+}$ ).

25

## EXAMPLE 51

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid

MS: 389 ( $M^{+1+}$ ).

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Analysis for  $C_{25}H_{28}N_2O_2 \cdot 0.2 H_2O$ : Calcd: C, 76.58; H, 7.30; N, 7.14. Found: C, 76.61; H, 7.29; N, 7.03.

#### EXAMPLE 52

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid

5 MS: 389 ( $M^{+1+}$ ).

Analysis for  $C_{25}H_{28}N_2O_2 \cdot 0.1 H_2O$ : Calcd: C, 76.93; H, 7.28; N, 7.18. Found: C, 76.85; H, 7.44; N, 7.06.

#### EXAMPLE 53

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid.

10 mp 171-177°C.

MS: 401 ( $M^{+1+}$ ).

Analysis for  $C_{26}H_{28}N_2O_2 \cdot 0.2 H_2O$ : Calcd: C, 77.27; H, 7.08; N, 6.93. Found: C, 77.09; H, 6.97; N, 6.96.

#### EXAMPLE 54

15 2-{4-[3-(3-Piperidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid.

mp 59-61°C.

MS: 415 ( $M^{+1+}$ ).

Analysis for  $C_{27}H_{30}N_2O_2 \cdot 0.3 H_2O$ : Calcd: C, 77.22; H, 7.34; N, 6.67. Found: C, 77.18; H, 7.25; N, 6.49.

#### EXAMPLE 55

20 {5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp 222-224°C.

MS: 391 ( $M^{+1+}$ ).

#### EXAMPLE 56

25 {5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp >250°C.

MS: 377 ( $M^{+1+}$ ).



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Analysis for  $C_{18}H_{20}N_2O_3S_2 \cdot 0.4 H_2O$ : Calcd: C, 56.34; H, 5.46; N, 7.30; S, 16.71. Found: C, 56.27; H, 5.18; N, 7.31; S, 16.74.

#### EXAMPLE 57

3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid. mp 214-215°C.

MS: 405 ( $M^{+1+}$ ).

#### EXAMPLE 58

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid. mp 152-154°C.

MS: 417 ( $M^{+1+}$ ), 418 ( $M^{+}$ ), 419 ( $M^{+1+}$ ).

Analysis for  $C_{21}H_{26}N_2O_3S_2 \cdot 0.2 H_2O$ : Calcd: C, 59.74; H, 6.30; N, 6.64; S, 15.19. Found: C, 59.59; H, 6.16; N, 6.52; S, 15.38.

#### EXAMPLE 59

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methyl-benzoic acid. mp 98-99°C.

MS: 414 ( $M^{+}$ ).

#### EXAMPLE 60

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulfonamide was prepared by reacting the product from Example 9 with methanesulfonamide. mp 53-61°C.

Analysis for  $C_{23}H_{22}Cl_2N_2O_3S \cdot 0.13 H_2O$ : Calcd: C, 57.58; H, 4.68; N, 5.84. Found: C, 57.20; H, 4.66; N, 5.51.

#### EXAMPLE 61

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp 214-216°C.

Analysis for  $C_{23}H_{22}N_2O_4 \cdot 0.25 H_2O$ : Calcd: C, 69.99; H, 5.74; N, 7.18. Found: C, 69.90; H, 5.82; N, 6.81.

Analysis for  $C_{22}H_{17}F_4NO_2$ : Calcd: C, 65.51; H, 4.25; N, 3.47. Found: C, 65.51; H, 4.13; N, 3.46.

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EXAMPLE 67

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid

mp 203-208°C.

Analysis for  $C_{21}H_{16}F_2N_2O_4$ : Calcd: C, 63.32; H, 4.05; N, 7.03.

5 Found: C, 62.94; H, 4.37; N, 6.87.

EXAMPLE 68

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine  
was prepared as described in Example 1, using a tetrazole fluoro intermediate that  
was synthesized from commercially available 2-fluorobenzonitrile and sodium  
10 azide under standard reaction conditions. mp 129 shrink, 152-157°C.

Analysis for  $C_{21}H_{17}Cl_2N_5 \cdot 0.15 \text{ EtOAc} \cdot 0.15 \text{ Hexane}$ : Calcd: C, 61.80; H, 4.64;  
N, 16.12. Found: C, 61.61; H, 4.28; N, 15.83.

EXAMPLE 69

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic  
15 acid. mp 190-193°C.

Analysis for  $C_{22}H_{16}F_4N_2O_4$ : Calcd: C, 58.93; H, 3.60; N, 6.25.

Found: C, 58.69; H, 3.42; N, 6.57.

EXAMPLE 70

2-(4-Phenethyl-phenylamino)-benzoic acid. mp 173-182°C.

20 Analysis for  $C_{21}H_{19}NO_2$ : Calcd: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.42;  
H, 5.97; N, 4.47. Found: C, 79.59; H, 6.03; N, 4.50.

EXAMPLE 71

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid.  
mp 180-182°C.

25 Analysis for  $C_{21}H_{16}Cl_2FNO_2 \cdot 0.06 \text{ H}_2\text{O}$ : Calcd: C, 62.23; H, 4.01; N, 3.46.  
Found: C, 61.83; H, 4.04; N, 3.29.

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## EXAMPLE 72

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid.

mp 168-171°C.

Analysis for  $C_{20}H_{16}Cl_2N_2O_2$ : Calcd: C, 62.03; H, 4.16; N, 7.23.

5 Found: C, 62.11; H, 4.17; N, 7.07.

## EXAMPLE 73

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 192.5-194.5°C.

Analysis for  $C_{21}H_{17}ClN_2O_4$ : Calcd: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.83;

10 H, 4.62; N, 6.79.

## EXAMPLE 74

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 210-212°C.

Analysis for  $C_{21}H_{17}ClN_2O_4 \cdot 0.26 H_2O$ : Calcd: C, 62.82; H, 4.40; N, 6.98.

15 Found: C, 62.51; H, 4.34; N, 6.58.

## EXAMPLE 75

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid.

mp 153-160°C.

Analysis for  $C_{22}H_{19}Cl_2NO_2 \cdot 0.61 H_2O$ : Calcd: C, 64.25; H, 4.96; N, 3.41.

20 Found: C, 63.87; H, 4.64; N, 3.55.

## EXAMPLE 76

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 236-238°C.

## EXAMPLE 77

25 2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 200.5-202.5°C.

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Analysis for  $C_{21}H_{16}Cl_2N_2O_4$ : Calcd: C, 58.49; H, 3.74; N, 6.50.

Found: C, 58.33; H, 3.67; N, 6.29.

#### EXAMPLE 78

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic  
5 acid. mp 130-132°C.

Analysis for  $C_{22}H_{16}Cl_2F_3NO_2$ : Calcd: C, 58.17; H, 3.55; N, 3.08.

Found: C, 58.25; H, 3.65; N, 3.05.

#### EXAMPLE 79

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.  
10 mp >260°C.

#### EXAMPLE 80

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dimethylamino-benzoic  
acid. mp 75-80°C.

#### EXAMPLE 81

2-{4-[2-(3,5-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid. mp 191-194°C.  
15 Analysis for  $C_{21}H_{17}Cl_2NO_2$ : Calcd: C, 65.30; H, 4.44; N, 3.63. Found: C, 65.38;  
H, 4.29; N, 3.52.

#### EXAMPLE 82

2-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-  
20 benzoic acid was prepared according to Example 1 using a decahydroisoquinoline  
aldehyde which was prepared from trans-decahydroisoquinoline and para-  
fluorobenzaldehyde under standard reaction conditions. mp 203-206°C.

Analysis for  $C_{30}H_{34}N_2O_2 \cdot 0.12 H_2O$ : Calcd: C, 78.89; H, 7.56; N, 6.13.

Found: C, 78.49; H, 7.58; N, 5.90.

25 The following examples are prepared according to the foregoing methods,  
or by utilizing standard combinatorial synthetic methodology by reacting halo  
substituted benzoate esters with a substituted aniline to form the corresponding

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diarylamine, followed by saponification to the benzoic acid of Formula I. The reactions are carried out on 0.15 mmol scale as follows. Solutions of each halo benzoate reactant (0.18 M) in toluene are placed in 2 dram reaction vials. Each aniline reactant is dissolved in anhydrous toluene to give 0.15 M solutions. A Distriman pipet is used to add 1 mL (0.15 mmol, 1 eq) of each halo benzoate solution to the appropriate vials containing 1 mL (0.18 mmol, 1.2 eq) of the aniline reactants. A catalyst solution is prepared by dissolving 0.025 M of  $\text{Pd}_2(\text{dba})_3$  (dipalladium-tridibenzylidene acetone) and 0.075 M of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) in toluene, and 0.25 mL of the catalyst solution is added to each reaction vial. A base, generally cesium carbonate (68 mg, 0.21 mmol, 1.40 eq) is added to each reaction vial, and the vials are capped and placed in a shaker oven and heated at 100°C for 48 hours. The reaction mixtures are then cooled, and the reaction solvents are removed by evaporation. The solid residue is suspended in 400  $\mu\text{L}$  of ethyl acetate and filtered to remove all catalyst. The filtrates are concentrated to dryness by evaporation to provide compounds of Formula I, wherein the benzoic acid portion is esterified (e.g., benzyl or methyl ester). The esters are dissolved in 500  $\mu\text{L}$  of THF/ethanol (1:1 v/v) to which is added 300  $\mu\text{L}$  of 5 M sodium hydroxide. The solutions are shaken for 5 hours at 60°C and then cooled and concentrated to dryness by evaporation of the solvents to provide the desired compounds of Formula I. Typical compounds prepared by this method are as follows. The structure of the compounds are generally confirmed by mass spectral analysis.

#### EXAMPLE 83

2-(3',5'-Dichloro-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 371; MW: 372.2495.

#### EXAMPLE 84

2-(3',5'-Dibromo-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 459; MW: 461.1515.

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## EXAMPLE 85

2-(4-1,3-Benzodioxol-5-yl-2-methyl-phenylamino)-benzoic acid

MS: 347; MW: 347.3683.

## EXAMPLE 86

5 2-(2,2',4'-Trichloro-biphenyl-4-ylamino)-benzoic acid

MS: 391; MW: 392.6678.

## EXAMPLE 87

2-(2-Chloro-3',4'-difluoro-biphenyl-4-ylamino)-benzoic acid

MS: 359; MW: 359.7578.

10

## EXAMPLE 88

2-(3'-Bromo-2-chloro-biphenyl-4-ylamino)-benzoic acid

MS: 401; MW: 402.6737.

## EXAMPLE 89

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid

15

## EXAMPLE 90

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

## EXAMPLE 91

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

## EXAMPLE 92

20

5-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid

## EXAMPLE 93

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

## EXAMPLE 94

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,5-dimethoxy-benzoic acid

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EXAMPLE 95

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 96

3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 97

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid

EXAMPLE 98

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 99

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid

EXAMPLE 100

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 101

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 102

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 103

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 104

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 105

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid



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EXAMPLE 106

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isindol-5-ylamino]-benzoic acid

EXAMPLE 107

5 2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 108

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid

EXAMPLE 109

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

10

EXAMPLE 110

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-6-nitro-benzoic acid

EXAMPLE 111

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid

15

EXAMPLE 112

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 113

20

{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine

EXAMPLE 114

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 115

3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

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EXAMPLE 116

2-{4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 159-161°C.

EXAMPLE 117

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monosodium; mp 107-108°C.

EXAMPLE 118

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monopotassium; mp >200°C.

10

EXAMPLE 119

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid calcium salt (1:1); mp >220°C.

EXAMPLE 120

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoate-2-hydroxy-1,1-bis-hydroxymethyl-ethyl-ammonium; mp 185-187°C.

EXAMPLE 121

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-methoxy-benzoic acid; mp 155-158°C.

EXAMPLE 122

20 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 184-185°C.

EXAMPLE 123

2-{3-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 155-157°C.

EXAMPLE 124

25 2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 182-184°C.

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 153-154°C.

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## EXAMPLE 135

2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 106-108°C.

## EXAMPLE 136

5 2-{4-[2-(4-{2-Hydroxycarbonylphenylamino}phenyl)ethyl]-phenylamino}-benzoic acid; MS 451 (M<sup>-1</sup>).

## EXAMPLE 137

2-(3',5'-Dichloro-biphenyl-4-ylamino)-benzoic acid; mp >220°C.

## EXAMPLE 138

10 4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-5-nitro-benzoic acid; mp 74-78°C.

## EXAMPLE 139

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-benzoic acid; mp 122-123°C.

15

## EXAMPLE 140

5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 182-184°C.

## EXAMPLE 141

20

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-C,C,C-trifluoro-methanesulfonamide; MS 531 (M<sup>-</sup>).

## EXAMPLE 142

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-benzenesulfonamide; MS 539.

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EXAMPLE 143

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid; mp 190-192°C. MS 453 ( $M^{-1}$ ).

EXAMPLE 144

5 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid; mp 264-266°C.

EXAMPLE 145

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid; mp 134-136°C; MS 454 ( $M^{+}$ ).

10

EXAMPLE 146

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid; MS 454 ( $M^{+}$ ).

EXAMPLE 147

15

2-((4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl)-methyl-amino)-5-dimethylamino-benzoic acid; mp 128-131°C.

EXAMPLE 148

2-((4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl)-methyl-amino)-benzoic acid; MS 400 ( $M^{+}$ ).

EXAMPLE 149

20

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid; MS 485 ( $M^{+}$ ).

EXAMPLE 150

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; MS 513 ( $M^{+}$ ).

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## EXAMPLE 151

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid;  
mp 106-110°C.

## EXAMPLE 152

5 2,2'-[1,2-Ethanediy]bis (4,1-phenyleneimino)]bis-benzoic acid

## EXAMPLE 153

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

## EXAMPLE 154

2-{3-[2-(4-Chlorophenyl)ethyl]phenylamino}-benzoic acid

10

## EXAMPLE 155

2-{3-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

## EXAMPLE 156

2-{3-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid

## EXAMPLE 157

15

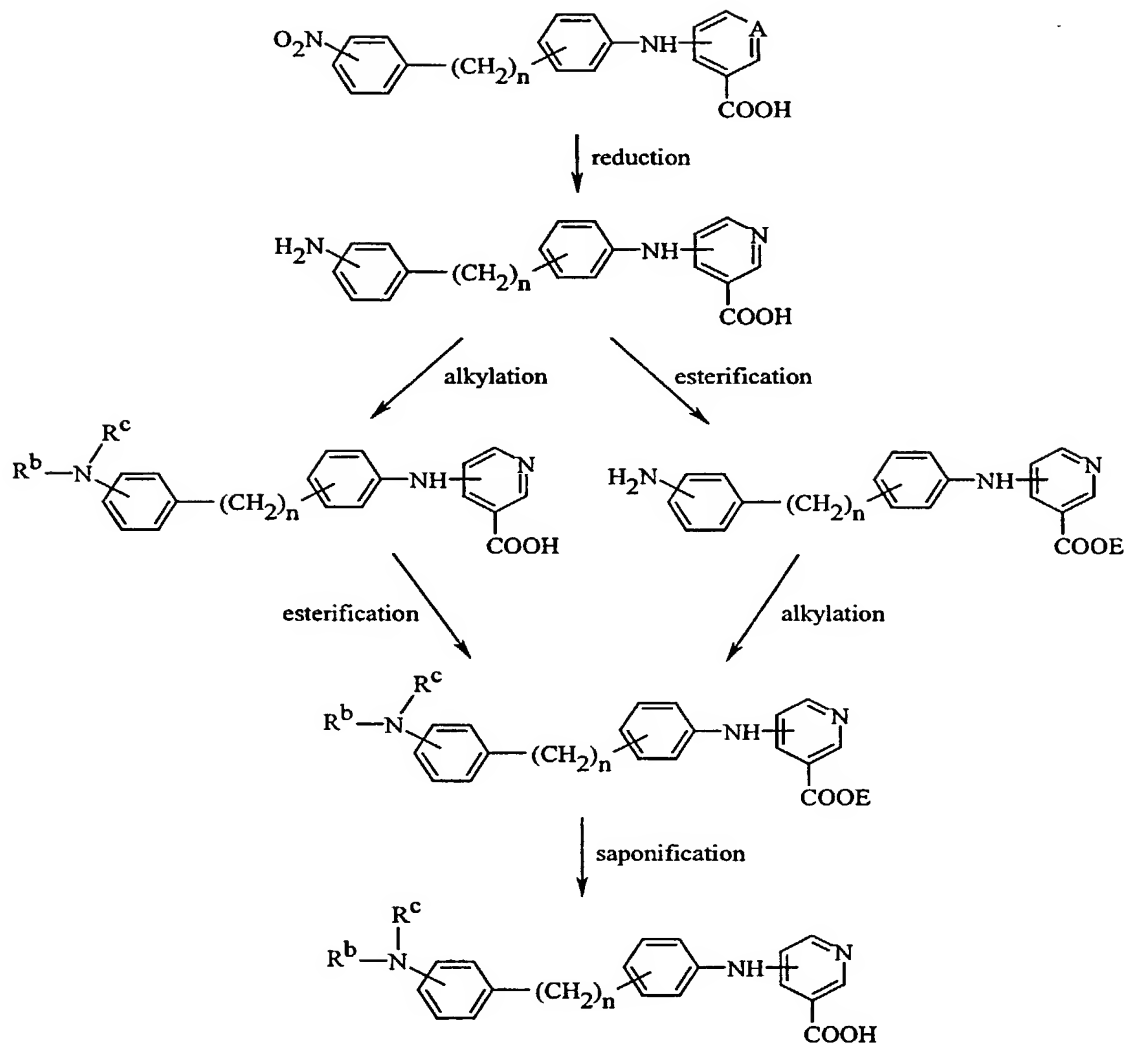
2-{3-[3-(4-Di-n-propylaminophenyl)propyl]phenylamino}-benzoic acid

20

The following Examples 158-163 illustrate the use of invention compounds as starting materials and intermediates in the synthesis of other invention compounds and derivatives. The examples illustrate reduction of nitro groups to amino groups, alkylation of amino group, and esterification of carboxylic acid groups. These reactions are depicted in the following generalized Scheme 12.

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Scheme 12



where  $\text{R}^b$  and  $\text{R}^c$  are as defined above, and E is an ester forming group such as  $\text{C}_1$ - $\text{C}_6$  alkyl (e.g., methyl, 2,2,2-trichloroethyl), benzyl, diphenylmethyl, or the like.

## EXAMPLE 158

## 2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid

To a slurry of 4-[3-(4-nitrophenyl)propyl]aniline (4.08 g, 15.9 mmol) and 2-bromobenzoic acid (3.52 g, 17.5 mmol) in i-PrOH (100 mL) was added

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Cu(OAc)<sub>2</sub> (87 mg, 0.478 mmol) and KOAc (3.44 g, 35.0 mmol) at room temperature. The resulting mixture was allowed to heat under reflux for 23 hours, then cooled to room temperature. After removing the solvent under reduced pressure, the residue was diluted with water (100 mL) and basified with aqueous 1.0 M-NaOH solution to pH 9.0. The aqueous layer was washed with Et<sub>2</sub>O (20 mL, twice) and acidified with aqueous 1.0 M-HCl solution to pH 3.0. The precipitate formed was filtered by suction and dried at 60°C in vacuo, affording the title compound as a beige solid (5.75 g, 96% yield). mp 150-153°C. MS (Fab): 376 (MH<sup>+</sup>).

#### EXAMPLE 159

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid

To a solution of 2-{4-[3-(4-nitrophenyl)propyl]phenylamino}benzoic acid (Example 158) (3.0 g, 7.97 mmol) in DMF (40 mL) was added 10% Pd-C (300 mg) at room temperature under argon atmosphere. Hydrogen gas (1 atm) was introduced into the flask and the mixture was stirred for 14 hours at room temperature. The reaction mixture was filtered through a Celite pad to remove Pd-C and concentrated in vacuo. The residue was diluted with MeOH (ca. 50 mL) and concentrated in vacuo. This operation was repeated 3 times to remove any trace of DMF. The residue was diluted with MeOH again, and insoluble stuff was removed by filtration. Removing the solvent of the filtrate in vacuo afforded an oil, which was diluted with CH<sub>3</sub>CN (50 mL) and added dropwise water (100 mL) slowly. The precipitate formed was filtered and dried at 60°C in vacuo, affording the title compound as a white solid (2.34 g, 85% yield). mp 110-112°C. MS (Fab): 347 (MH<sup>+</sup>).

#### EXAMPLE 160

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid methyl ester

To a solution of 2-{4-[3-(4-aminophenyl)propyl]phenylamino}benzoic acid (Example 159) (2.34 g, 6.75 mmol) in MeOH (50 mL) was added concentrated H<sub>2</sub>SO<sub>4</sub> (1.0 mL) at room temperature. The mixture was stirred under reflux for 3.0 days. The reaction was quenched with Et<sub>3</sub>N (10 mL) at 5°C, and the



2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

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To an emulsion of 2-{4-[3-(4-diethylaminophenyl)propyl]phenylamino}-benzoic acid methyl ester (1.68 g, 4.03 mmol) in EtOH (50 mL) was added aqueous 3 M-KOH solution (4.0 mL, 12.0 mmol) at room temperature, then the mixture was allowed to heat under reflux for 40 minutes. The reaction mixture was cooled to room temperature and neutralized with aqueous 1.0 M-HCl solution to pH 9.0. The mixture was concentrated under reduced pressure to remove EtOH, and the resulting aqueous solution was extracted with CHCl<sub>3</sub> (50 mL, 3 times). The combined extract was washed with brine (10 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and purification by column chromatography (silica gel 60N, conc NH<sub>4</sub>OH/MeOH/CHCl<sub>3</sub> 0.2:2:100 to 0.5:5:100) afforded a yellow oil. This oil was diluted with acetone, and the solution was concentrated under reduced pressure at room temperature to give the title compound as an amorphous solid (1.62 g, 99% for 0.2 hydrate).

MS (Fab): 403 (MH<sup>+</sup>).

Analysis for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.20 H<sub>2</sub>O: Calcd: C, 76.89; H, 7.54; N, 6.90.

Found: C, 76.73; H, 7.67; N, 7.10.

#### EXAMPLE 163

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid

The title compound was prepared from 2-{4-[3-(4-ethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester (from Example 161), EtOH (10 mL), and 3 M-KOH solution (1.0 mL) using the procedure described in Example 162. This procedure yielded a yellow solid, 253 mg of the desired product (90% for 0.1 hydrate).

MS (Fab): 375 (MH<sup>+</sup>).

Analysis for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>·0.10 H<sub>2</sub>O: Calcd: C, 76.61; H, 7.02; N, 7.44.

Found: C, 76.62; H, 7.06; N, 7.36.

## BIOLOGICAL EXAMPLES

Representative compounds of Formula I have been evaluated in several in vitro and in vivo assays which are well-established as indicative of clinical usefulness in treating Alzheimer's disease.

### 5 AMYLOID ASSAYS

#### BASSR (Beta-Amyloid Self-Seeding Radioassay)

An assay for inhibitors of self-seeded amyloid fibril growth

#### **Materials:**

#### Stock Solutions:

10 *Assay Buffer* - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN<sub>3</sub>,  
1 M urea (filter and store at 4°C).

*Soluble A $\beta$ (1-40) peptide* (Bachem, Torrance, CA) - 2.2 mg/mL in deionized H<sub>2</sub>O  
(stored in aliquots at -20°C, keep on ice when thawed) will self-seed after 1 week  
storage. Typically, the solution should be stored until no lag phase is seen in the  
15 assay.

*<sup>125</sup>I-labeled A $\beta$ (1-40)* - 150K-350K cpm/ $\mu$ L in 100% acetonitrile - 0.1%  
trifluoroacetic acid (TFA) - 1%  $\beta$ -mercaptoethanol (aliquots stored at -20°C).  
*<sup>125</sup>I-labeled A $\beta$ (1-40)* can be made in accordance with the procedure set forth by  
H. LeVine, III in *Neurobiol. Aging*, 16, 755, (1995), which is hereby incorporated  
20 by reference, or this reagent may be purchased from Amersham, Arlington  
Heights, Illinois.

*Final assay conditions:* 30  $\mu$ M soluble A $\beta$ (1-40) in deionized water in assay  
buffer + 20K-50K cpm <sup>125</sup>I-labeled A $\beta$ (1-40) per assay. Compound to be tested  
is dissolved in dimethylsulfoxide (DMSO), typically 5 to 50 mM stock, such that  
25 the final concentration of DMSO is <1% v/v in the assay.

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**Assay:** Reaction mixture for 50 assays (on ice) is comprised of 0.1 to 0.2  $\mu\text{L}$  of  $^{125}\text{I}$ -labeled A $^{125}\text{I}$ -labeled  $A\beta$  (1-40) + 1  $\mu\text{L}$  of soluble  $A\beta$  (1-40) + 13.5  $\mu\text{L}$  assay buffer per assay. The following are the amounts of the components of the reaction mixture sufficient for 50 assay wells:

- 5                    5-10  $\mu\text{L}$   $^{125}\text{I}$ -labeled  $A\beta$  (1-40) dried down
- 675  $\mu\text{L}$  assay buffer
- 50  $\mu\text{L}$  soluble  $A\beta$  (1-40)

#### Assay Method

- 1) Prepare reaction mixture above by mixing components and storing on ice.
- 10        2) Pipet 14.5  $\mu\text{L}$  of reaction mixture into each of 50 wells on a polypropylene U-bottom 96-well microtiter plate on ice. (Costar 3794).
- 3) Add 1.7  $\mu\text{L}$  of diluted compound to be tested to each well in a column of eight, including solvent control. Serial 3-fold dilutions from 1 mM (100  $\mu\text{M}$  final) in assay buffer - urea = 7 dilutions + zero. Each 96-well plate can
- 15        therefore accommodate 11 samples + 1 Congo Red control (0.039-5  $\mu\text{M}$  final in 2-fold steps).
- 4) Seal the plate with aluminum film (Beckman 538619) and incubate for 10 minutes on ice.
- 5) Raise the temperature to 37°C and incubate for 3 to 5 hours (depending on
- 20        the lot of the peptide).
- 6) Remove the aluminum film and add 200  $\mu\text{L}$ /well of ice cold assay buffer with urea, collecting the radiolabeled fibrils by vacuum filtration through 0.2  $\mu\text{m}$  pore size GVWP filters in 96-well plates (Millipore MAGV N22, Bedford, MA). Determine the radioactivity of the filters using standard
- 25        methods well-known to those skilled in the art.

#### BASST (Beta-Amyloid Self-seeding, ThioflavinT)

An assay for inhibitors of self-seeded amyloid fibril growth

#### METHODS:

##### **Materials:**

- 30        Stock Solutions:

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*Assay Buffer* - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN<sub>3</sub>,  
1 M urea (filter and store at 4°C)

*Soluble Aβ (1-40)* - 2.2 mg/mL in deionized H<sub>2</sub>O (store in aliquots at -20°C, keep  
on ice when thawed) will self-seed after 1 week storage. Typically, the solution  
should be stored until no lag phase is seen in the assay.

*Final assay conditions:* 30 μM soluble Aβ (1-40) in deionized water in assay  
buffer. Compound to be tested is dissolved in DMSO, typically 5 to 50 mM stock,  
such that the final concentration of DMSO is <1% v/v in the assay.

**Assay:** Reaction mixture for 50 assays (on ice) comprised of 1 μL of soluble  
Aβ (1-40) + 13.5 μL assay buffer per assay. The following are the amounts of the  
components of the reaction mixture that result in each of the 50 assay wells:

50 μL soluble Aβ (1-40)

675 μL assay buffer

#### Assay Method

- 1) Prepare the reaction mix above by mixing the components and storing on ice.
- 2) Pipet 14.5 μL of reaction mixture into each of 50 wells of a polystyrene U-bottom 96-well microtiter plate (Corning 25881-96) on ice.
- 3) Add 1.7 μL of diluted compound to be tested to each well in a column of eight, including solvent control. Serial 3-fold dilutions from 1 mM (100 μM final) in assay buffer - urea = 7 dilutions + zero. Each 96-well plate can therefore accommodate 11 samples + 1 Congo Red control (0.039-5 μM final in 2-fold steps).
- 4) Seal the plate with aluminum film and incubate for 10 minutes on ice.
- 5) Raise the temperature to 37°C and incubate for 3 to 5 hours (depends on the lot of the peptide).
- 6) Remove the aluminum film and add 250 μL/well of 5 μM thioflavin T (ThT) [T-3516, Sigma-Aldrich] in 50 mM glycine-NaOH, pH 8.5. Read

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fluorescence on a plate reader (ex = 440 nm/20 nm ; em = 485 nm/20 nm)  
within 5 minutes.

#### **BAPA (Beta-Amyloid Peptide Aggregation)**

This assay is used to provide a measure of inhibition by a compound  
5 against the aggregation behavior of the beta amyloid peptide.

The purpose of this assays is to provide a higher volume method of  
assaying the amount of beta amyloid aggregation using an endpoint assay based  
on filtration. In this assay, hexafluoroisopropanol (HFIP) is used to break down  
the initial amyloid peptide to a monomer state and use a concentration of 33  $\mu$ M  
10 which is high enough so that aggregation will occur at pH 6.0 in several hours.

#### **METHODS:**

##### **$\beta$ -Amyloid Peptide Aggregation, pH 6.0 (BAPA)**

In a 96-well plate (Costar 3794), we add 25  $\mu$ L 50 mM Phosphate Buffer,  
pH 6.0, 10  $\mu$ L 0.5 mg/mL A $\beta$  (1-40) peptide in 20% HFIP + 0.1  $\mu$ L/assay  
15 radioiodinated  $^{125}$ I A $\beta$  (1-40) [ $^{125}$ I A $\beta$ (1-40)], and 1  $\mu$ L of the compound to be  
tested starting at 50 mM with a concentration of DMSO <1%. Then, we incubate  
for 2 to 4 hours at room temperature. We stop the reaction with 200  $\mu$ L of 50 mM  
phosphate buffer, pH 6.0, and filter it through a 0.2  $\mu$ m 96-well filter plate  
(Millipore MAGU N22). We wash the filter plate with 100  $\mu$ L of the same  
20 phosphate buffer. Aggregation was detected on a Microbeta counter after  
impregnating the filters with Meltilex (1450-441) and is corrected for background.

#### **BATYM ASSAY**

#### **METHODS:**

Required A $\beta$  (1-42) (California Peptide) was dried from its  
25 hexafluoroisopropanol (HFIP) stock solution. The A $\beta$  (1-42) was dissolved in  
dimethylsulfoxide (DMSO) and then mixed with phosphate buffered saline (PBS)  
(pH 7.4). The mixed A $\beta$  (1-42) solution was filtered with a 0.2  $\mu$ m Omnipore  
membrane syringe filter (Millipore, Bedford, MA). The compound to be tested in  
DMSO (50 times concentrate) was put into each well (0.5  $\mu$ L/well) of a 96-well

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plate. The A $\beta$  (1-42) solution was added into each well (24.5  $\mu$ L/well). The plate was centrifuged at 1,000 g for 5 minutes and incubated at 37°C for 1 day (A $\beta$  1-42; final concentration 100  $\mu$ M).

After incubation Thioflavin T (ThT) (30  $\mu$ M) solution in glycine-NaOH buffer (pH 8.5, 50 mM) was added into each well (250  $\mu$ L/well), fluorescence was measured (ex = 440/20 nm, em = 485/20 nm) using a fluorescence plate reader. The inhibitory activity was calculated as the reduction of fluorescence with the following formula:

$$\text{Inhibition (\%)} = \{F(A\beta) - F(A\beta + \text{compound})\} / \{F(A\beta) - F(\text{solvent} + \text{compound})\} \times 100$$

The IC<sub>50</sub>s were calculated by a curve fitting program using the following equation. The data were obtained from two different experiments in triplicate.

$$\text{Inhibition}(x) = 100 - 100 / \{1 + (x/IC_{50})^n\},$$

x = Concentration of tested compound (M),

IC<sub>50</sub> = (M),

n = Hill coefficient.

Representative compounds of Formula I have exhibited inhibitory activities (IC<sub>50</sub>) ranging from 0.1  $\mu$ M to greater than 100  $\mu$ M in the foregoing assays.

The results of these assays for specific and representative compounds of the present invention are shown in Table 1 below.

Table 1.  $\beta$ -Amyloid Inhibitory Activity of Compounds of Formula I

Example No.	BASSR (IC <sub>50</sub> = $\mu$ M)	BASST (IC <sub>50</sub> = $\mu$ M)	BATYM (IC <sub>50</sub> = $\mu$ M)	BAPA (IC <sub>50</sub> = $\mu$ M)
1	10 (P), >100 (P) (6 $\times$ ), >100 (Q), >100 (R), >100 (S), 52 (T) >100 (Z)	2, 4, 30, 10 (P) 3(Q) >100 (R) 11 (S), 11 (T) 6(Z)	50, 58.8 (P) 57.8 (Q)	60 (P), >100 (P) 86 (Q), >60 (R), >60 (S), 11 (T)
2	2.2, 4.1, 4.1, 12, 4.5	1, 1.5 (P)	6.52 (P)	70 (P)
3	4.5, 5, 5 (all 3 V-shaped) (P) 15 (ppt), 5 (Q)	2 (P) 3 (Q)	11.7 (P)	>60 (P)
4	30, >100 (3 $\times$ )	3, 4, 8	26.3, 30.7	67
5	70, >100	4.5	10	74
6	15, 21, 20, 40	4, 1, 3	21.5	>60
7	18, 13, 12, 20	2	8.83	39
8	15, 15, 18, 15	3, >100	7.17	
9	20 (ppt), 30, 52, 40 (P)	1, 2 (P)	20.1, 28.2 (P) 38.6 (R)	75 (P)
10	70, 50	4	75.7	67
11	18 (ppt), 20 (ppt), 20 (2 $\times$ ), >100 (P) >100, 21, 30 (Q)	1, 1, 3 (P) 1, 0.8 (Q)	5.62 (P) 6.78 (Q)	23 (P) 9 (Q)
12	20 (4 $\times$ )	1, 1	3.93	>60
13	21, >100, 20 (ppt), 15 (ppt), >100	0.9	6.41	6
14	18 (ppt), 8, 6 (ppt), 7 (ppt)	1.0	10.9	>10 (V-shaped)
15	100 (3 $\times$ ) P 100, 16 (V-shaped) 12, 15, 11 (Q)	1 (P) 1.2 (Q)	8.52 (P) 7.26 (Q) 7.07 (Q)	>60 (P) 7 (Q)



Table 1.  $\beta$ -Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC <sub>50</sub> = $\mu$ M)	BASST (IC <sub>50</sub> = $\mu$ M)	BATYM (IC <sub>50</sub> = $\mu$ M)	BAPA (IC <sub>50</sub> = $\mu$ M)
16	18, 7.5, 10 (P) 70, 32, 42 (Q)	3, 0, 3 (P) 1.1, 0.8, 0.6 (Q)	12 (P) 10.3 (Q)	13 (P)
17	>100 (ppt) (3 $\times$ )	6.2	64.5	>60 (Q), 41 (R)
18	>100 (5 $\times$ ) (P)	30, >100 (P)	>100 (P)	9, >40, 53 (P), 12
19	3, 4, >100, 2.2	>100, 1, 1, 1.5	31.0, 34.0	>60, 43
20	4.2	6	68.6	22
21	3	4	62.7	26
22	3	9	>100	24
23	20	2	>100	17
24	>100	20	>100	91
25	>100	4	21.1	47
26	>100	1	>100	57
27	>100	3	19.8	74
28	>100	5	42.3	27
29	>100	4	38.1	30
30	30, 20	4, 2	75.3	38
31	>100	1	22.6	86
32	>100	1	29.2	96
33	>100	>100	>100	>10
34	45	3	45.0	48
35	>100	100	>100	154
36	>100	>100	>100	149
37	>100	0.8	30.2	25
38	20, 10 (V)	3	23.4	184
39	>100	20	>100	21
40	>100	3.0	>100	53
41	>100	5	49.7	42
42	>100	2	55.6	30
43	>100	0.3	24.2	63
44	>100	1	26.5	52
45	>100	1	21.5	32
46	>100	6	34.3	
47	>100	2	38.2	
48	25	10	>100	
49	>100	>100	>100	
50	>100	>100	>100	
51	85	0.8	39.1	

Example	BASSR	BASST	BATYM	BAPA
No.	(IC <sub>50</sub> = μM)	(IC <sub>50</sub> = μM)	(IC <sub>50</sub> = μM)	(IC <sub>50</sub> = μM)
52	75	0.5	36.5	
53	>100	0.3	30.0	
54	>100	0.4	43.9	
55	12	2	5.1	101
56	>100	3	11.5	30
57	4.8	1.5	4.0	50
58	3.5	1	5.1	60
59	>100	>100	>100	3
60	>100	3	40.7	8
61	18, 7.5, 10	3, 0.3	12	13
62	>100	1.5	8.98	
63	15, 15, 18 (ppt)	1	9.43	45
64	>100	5	35	>100
65	60, 80	1.5	15.9	>100 (V-shaped)
66	>100 (ppt), >100 (ppt)	2.1	50.1	>100
67	41	4	13.3	>60
68	>100, >100	1	>100	110
69	2 (V-shaped), 3.5 (ppt)	0.8	11.7	58
70	20, 100	10	>100	65
71	>100	3		>60
72	40, 15, 12	2, 2.5	74.8	>60, >60
73	25, 35, 40	0.3	9.43	>60
74	6, 18, 19, 18	0.3, 0.5	8.36	>60
75	>100	2.2	46.2	>60
76	3	0.5	8.59	>60
77	18, 15	8, 0.3	9.49	>60
78	70	0.1	>100	8
79	3.1, 50, 38, 70, 70, 30, 40	1, 0.3, 0.3, 0.3	9.14	51
80	>100	4	24.8	>60
81	>100	15	48.4	73
82	>100, >100, >100	2, 0.3, 0.3		
83	>100	>100		9, 47, 29
84	>100	>100		5, 40, 21
85	>100	18		8, 77, 45

Table 1.  $\beta$ -Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC <sub>50</sub> = $\mu$ M)	BASST (IC <sub>50</sub> = $\mu$ M)	BATYM (IC <sub>50</sub> = $\mu$ M)	BAPA (IC <sub>50</sub> = $\mu$ M)
86	40	18		>10, 89, 37
87	>100	50		>10, 15, 32
88	>100	10		>10, 37, 27
116	>100, >100	18, 30		96
117	>100	3	61.3	>100
118	>100, >100	6		>60
119	>100	3		>60
120	>100	3		>60
121	>100, >100	1		
122	>100	2	>100	>60
123	>100 (3 $\times$ ), 14 4, 18, >100, >100 (Q)	3, 3 3.2, 4 (Q)	70.8 85.2 (Q)	>60 (Q)
124	>100	10	62.7	
125	82	10	>100	80
126	>100, >100 30, 100 (Q)	4, 5 10, 4 (Q)	84 73.9 (Q)	63 >60 (Q)
127	>100 (ppt)	10	>100	67
128	>100 (ppt) (4 $\times$ ) 11, >100 (3 $\times$ ) 15, 20, 10, 7.5 (Q) 15, >100 (3 $\times$ ) Q	10, 41, 6 7, 3, 3 (Q)	75 >60 (Q)	60 >60 (Q)
129	1 (V-shaped) (2 $\times$ ) >100 (ppt)	10, 3, 2, 2	>100	>102
130	>100 (3 $\times$ )	2, >100, 50	47.5	238
131	>100	10	93.5	>60
132	>100	10	>100	60
133	>100	>100	>100	>60
134	>100	2	36.5	>60
135	>100	1.2	31.2	>60
136	>100	3	>100	53
137	>100, >100	3		52
141	>100	7	56.7	>50
142	>100	2.1	26.9	55
143	>100 (4 $\times$ )	40, 30	>100	2, >60, >60
144	15, 25	40	>100	114

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Table 1.  $\beta$ -Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC <sub>50</sub> = $\mu$ M)	BASST (IC <sub>50</sub> = $\mu$ M)	BATYM (IC <sub>50</sub> = $\mu$ M)	BAPA (IC <sub>50</sub> = $\mu$ M)
145	10, 40, 30	4	56.8	9
146	>100	30	>100	>60
147	>100	10	93.4	>60
148	>100		>100	
149	>100	>100	>100	>60
150	>100	10	>100	76
151	>100, >100	5, >100	>100	108
154	>100	3, 30	70.8	
155	>100	3	44.6	
156			27.8	
157			25.9	

A letter in parentheses after particular value indicates the particular synthetic lot of the compound tested. The terms "P," "Q," "R," "S," "T," and "Z" designate different lots of the same compound. For example, 10 (P) indicates that compound tested was from Lot P. If no lot is specified, the lot of the compound was Lot P.

The abbreviation "ppt" means precipitate and indicates that a precipitate formed at the indicated concentration. In addition, the term "V-shaped" means that inhibition was observed followed by precipitation.

A value followed by a number and  $\times$  (i.e., 4 $\times$ ) means that the compound was tested four times, and each time the result was the same.

The invention compounds have also shown good activity in standard in vivo assays commonly used to evaluate agents to treat diseases related to aggregation of amyloid proteins, especially Alzheimer's disease and other amyloidoses. In one assay, amyloid protein is induced into the spleen of mice by subcutaneous injections of silver nitrate, Freund's complete adjuvant, and an intravenous injection of amyloid enhancing factor. Silver nitrate is administered each day through Day 11. Test compounds are administered to the mice daily starting on Day 1 through Day 11. On Day 12, the animals are sacrificed, and the spleens are removed, histologically prepared, stained with Congo red, and the percent area of the spleen occupied by birefringent, Congo red-stained amyloid is

The above data establishes that representative invention compounds are active in standard assays used to measure inhibition of protein aggregation. The compounds exhibit excellent specificity, for example, as shown in the BASST assay, as well as the BATYM and BAPA assays. The compounds are thus useful to clinically inhibit amyloid protein aggregation and to image amyloid deposits for diagnostic use. The compounds will be used in the form of pharmaceutical formulations, and the following examples illustrate typical compositions.

EXAMPLE 164

Tablet Formulation

Ingredient	Amount
Compound of Example 1	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

The compound of Example 1 is mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for prevention of amyloid protein aggregation and treatment of Alzheimer's disease.

EXAMPLE 165

Parenteral Solution

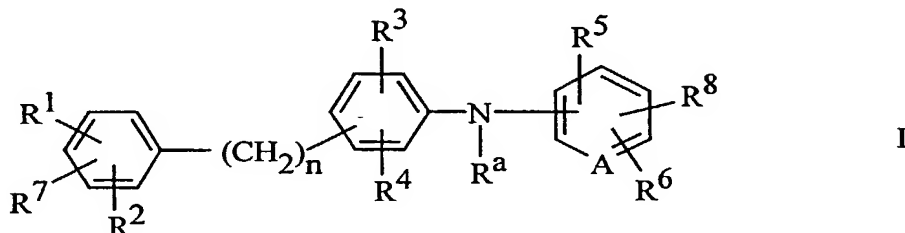
In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of Compound No. 19 (Example 19). The mixture is stirred and the pH is adjusted to 5.5 with hydrochloric acid. The volume is adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampoules, each containing 2.0 mL (40 mg of Compound No. 19), and sealed under nitrogen. The solution is administered by injection to a patient suffering from medullary carcinoma of the thyroid and in need of treatment.

The invention and the manner and process of making and using it, are now described in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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CLAIMS

What is claimed is:

1. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



wherein

$\text{R}^a$  is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or  $\text{-CC}_1\text{-C}_6$  alkyl;

$n$  is 0 to 5 inclusive;

$\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ , and  $\text{R}^7$  are independently hydrogen, halogen, -OH, -NH<sub>2</sub>,  $\text{NR}^b\text{R}^c$ , -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, -NO<sub>2</sub>, -OC<sub>1</sub>-C<sub>12</sub> alkyl, -C<sub>1</sub>-C<sub>8</sub> alkyl, -CF<sub>3</sub>, -CN, -OCH<sub>2</sub> phenyl, -OCH<sub>2</sub>-substituted phenyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl,  $\text{-O(CH}_2)_p\text{NR}^b\text{R}^c$ ,  $\text{-CNR}^b\text{R}^c$ ,  $\text{-NHCR}^b$ ,  $\text{-NH(CH}_2)_p\text{NR}^b\text{R}^c$ ,  $\text{-N(C}_1\text{-C}_6\text{alkyl)(CH}_2)_p\text{NR}^b\text{R}^c$ ,

$\text{-CH}\begin{matrix} \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \\ \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \end{matrix}$  ;

$\text{R}^8$  is COOH, tetrazolyl, -SO<sub>2</sub>R<sup>d</sup>, or -CONHSO<sub>2</sub>R<sup>d</sup>;

$\text{R}^b$  and  $\text{R}^c$  are independently hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, or

$\text{R}^b$  and  $\text{R}^c$  taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidiny, pyrrolol,



-OCH<sub>2</sub>- substituted phenyl, pyrrolyl, or -N(phenyl)<sub>2</sub>.

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5. The method of Claim 1 wherein

$R^a$  is hydrogen;

$n$  is 3, 4, or 5;

$R^3$  and  $R^4$  are hydrogen; and

$R^1$ ,  $R^2$ , and  $R^7$  are independently chlorine or hydrogen.

6. The method of Claim 1 wherein

$R^a$  is hydrogen;

$n$  is 2;

$R^3$  and  $R^4$  are hydrogen; and

$R^5$ ,  $R^6$ , and  $R^8$  are independently hydrogen,  $-\text{CO}_2\text{H}$ ,  $-\text{NO}_2$ ,  $-\text{OCH}_3$ ,

imidazolyl,  $-\text{CN}$ , fluorine,  $-\text{CH}_3$ ,  $-\text{CF}_3$ , halogen,

$-\text{NH}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{N}(\text{C}_1-\text{C}_6\text{alkyl})_2$ ,  $-\text{NH}_2$ , or pyrrolyl.

7. The method of Claim 1 wherein

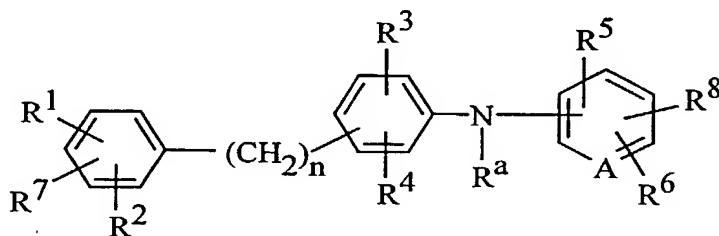
$R^a$  is hydrogen;

$n$  is 2;

$R^3$  and  $R^4$  are hydrogen; and

$R^5$  is  $-\text{CO}_2\text{H}$ .

8. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



wherein

$R^a$  is hydrogen;

$n$  is 1 to 5 inclusive;

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R<sup>3</sup> and R<sup>4</sup> are hydrogen;

R<sup>1</sup>, R<sup>7</sup>, and R<sup>2</sup> are independently chlorine, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -OH, CH<sub>3</sub>-,  
fluorine, -CF<sub>3</sub>, phenyl, hydrogen, -OCH<sub>2</sub> phenyl,  
-O(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -O phenyl, -O(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>,  
-CH(CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, pyrrolyl, -CH=CH-phenyl,  
-N[(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>]<sub>2</sub>, substituted phenyl, -OCH<sub>2</sub>-substituted phenyl,  
pyrazolyl, or -N(phenyl)<sub>2</sub>;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, -CO<sub>2</sub>H, -NO<sub>2</sub>, -OCH<sub>3</sub>,  
imidazolyl, -CN, fluorine, -CH<sub>3</sub>, -CF<sub>3</sub>, or pyrrolyl;

R<sup>8</sup> is COOH or tetrazolyl;  
or the pharmaceutically acceptable salts thereof.

9. The method of Claim 1 wherein the compound of Formula I is:

2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino]-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic  
acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic  
acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-  
1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-  
benzoic acid;

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- 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-  
3,5-dinitrobenzoic acid;  
2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic  
acid;  
5 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;  
2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;  
2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-  
benzoic acid;  
10 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-  
benzoic acid;  
2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-  
benzoic acid;  
2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;  
15 5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;  
2-(4-Phenethyl-phenylamino)-benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-  
benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic  
20 acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-  
benzoic acid;  
4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic  
acid;  
25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
methanesulfonyl-benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-  
yl-benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-  
30 benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-  
benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

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2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

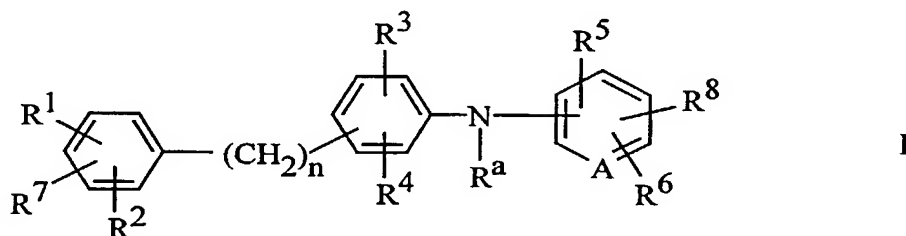
2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; or

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

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10. A method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



wherein

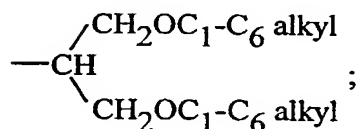


$R^a$  is hydrogen,  $C_1$ - $C_6$  alkyl, or  $-CC_1$ - $C_6$  alkyl;

$n$  is 0 to 5 inclusive;

$R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ , and  $R^7$  are independently hydrogen, halogen,  $-OH$ ,  $-NH_2$ ,  $NR^bR^c$ ,  $-CO_2H$ ,  $-CO_2C_1$ - $C_6$  alkyl,  $-NO_2$ ,  $-OC_1$ - $C_{12}$  alkyl,  $-C_1$ - $C_8$  alkyl,  $-CF_3$ ,  $-CN$ ,  $-OCH_2$  phenyl,  $-OCH_2$ -substituted phenyl,  $-(CH_2)_m$ -phenyl,  $-O$ -phenyl,  $-O$ -substituted phenyl,

15  $-CH=CH$ -phenyl,  $-O(CH_2)_pNR^bR^c$ ,  $-CNR^bR^c$ ,  $-NHCR^b$ ,  $-NH(CH_2)_pNR^bR^c$ ,  $-N(C_1$ - $C_6$ alkyl) $(CH_2)_pNR^bR^c$ ,



20  $R^8$  is  $COOH$ , tetrazolyl,  $-SO_2R^d$ , or  $-CONHSO_2R^d$ ;

$R^b$  and  $R^c$  are independently hydrogen,  $-C_1$ - $C_6$  alkyl,  $-(CH_2)_m$ -phenyl, or

$R^b$  and  $R^c$  taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidiny, pyrrolyl, imidazolyl, piperazinyl, 4- $C_1$ - $C_6$  alkylpiperazinyl, morpholino, 25 thiomorpholino, decahydroisoquinoline, or pyrazolyl;

- 25            14.      The method of Claim 10 wherein



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$R^a$  is hydrogen;

$n$  is 3, 4, or 5;

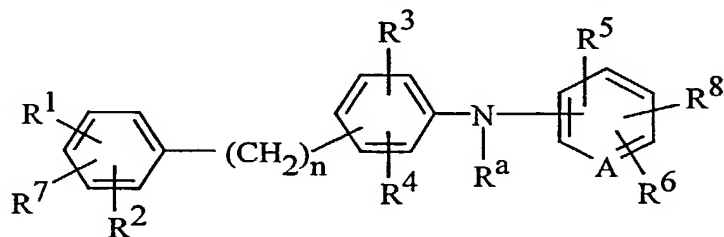
$R^3$  and  $R^4$  are hydrogen; and

$R^1$ ,  $R^2$ , and  $R^7$  are independently chlorine or hydrogen.

- 5      15.    The method of Claim 10 wherein  
           $R^a$  is hydrogen;  
           $n$  is 2;  
           $R^3$  and  $R^4$  are hydrogen; and  
           $R^5$  and  $R^6$  are independently hydrogen,  $-\text{CO}_2\text{H}$ ,  $-\text{NO}_2$ ,  $-\text{OCH}_3$ ,  
 10            imidazolyl,  $-\text{CN}$ , fluorine,  $-\text{CH}_3$ ,  $-\text{CF}_3$ , halogen,  
           $-\text{NH}-\text{C}_1-\text{C}_6$  alkyl,  $-\text{N}(\text{C}_1-\text{C}_6\text{alkyl})_2$ ,  $-\text{NH}_2$ , or pyrrolyl.

16.    The method of Claim 10 wherein  
           $R^a$  is hydrogen;  
           $n$  is 2;  
 15             $R^3$  and  $R^4$  are hydrogen; and  
           $R^8$  is  $-\text{CO}_2\text{H}$ .

17.    A method of inhibiting the aggregation of amyloid proteins to form  
          amyloid deposits, the method comprising administering to a patient in  
          need of inhibition of the aggregation of amyloid protein an amyloid  
 20            protein aggregation inhibiting amount of a compound of Formula I



I

wherein

$R^a$  is hydrogen;

$n$  is 1 to 5 inclusive;

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R<sup>3</sup> and R<sup>4</sup> are hydrogen;

R<sup>1</sup>, R<sup>7</sup>, and R<sup>2</sup> are independently chlorine, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -OH, CH<sub>3</sub>-,

fluorine, -CF<sub>3</sub>, phenyl, hydrogen, -OCH<sub>2</sub> phenyl,

-O(CH<sub>2</sub>)<sub>3</sub>N(CH<sub>3</sub>)<sub>2</sub>, -O phenyl, -O(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>,

5 -CH(CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, pyrrolyl, -CH=CH-phenyl,

-N[(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>]<sub>2</sub>, substituted phenyl, -OCH<sub>2</sub>-substituted phenyl,

pyrazolyl, or -N(phenyl)<sub>2</sub>;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, -CO<sub>2</sub>H, -NO<sub>2</sub>, -OCH<sub>3</sub>,

imidazolyl, -CN, fluorine, -CH<sub>3</sub>, -CF<sub>3</sub>, or pyrrolyl;

10 R<sup>8</sup> is COOH or tetrazolyl;

A is CH or N;

R<sup>1</sup> and R<sup>2</sup>, when adjacent to one another, can be methylene-dioxy;  
or the pharmaceutically acceptable salts thereof.

18. The method of Claim 17 wherein the compound of Formula I is:

15 2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino]-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic  
acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;

20 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino} benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic  
acid;

25 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-  
1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino} benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid;

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2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-  
benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-  
3,5-dinitrobenzoic acid;

5 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic  
acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-  
5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

10 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-  
benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-  
benzoic acid;

15 2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-  
benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic  
acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-  
benzoic acid;

25 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic  
acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
methanesulfonyl-benzoic acid;

30 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-  
yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-  
benzoic acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-  
benzoic acid;

5 5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-  
benzoic acid;

10 6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-  
benzoic acid;

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-  
benzoic acid;

20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-  
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-  
trifluoromethyl-benzoic acid;

25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-  
benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

30 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-  
phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic  
acid;

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2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-  
 phenylamino)-benzoic acid;  
 5 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic  
 acid;  
 10 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic  
 acid;  
 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-  
 benzoic acid;  
 15 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-  
 phenylamino)-benzoic acid;  
 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic  
 acid;  
 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic  
 acid;  
 20 2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-  
 phenylamino)-benzoic acid;  
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic  
 acid;  
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-  
 25 nitrobenzoic acid;  
 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-  
 benzoic acid; or  
 2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

19. The compounds:

30 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

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2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;  
 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic  
 acid;  
 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-  
 1-yl-5-nitrobenzoic acid; or  
 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid.

20. The compounds:

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-  
 benzoic acid;  
 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-  
 dinitrobenzoic acid;  
 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic  
 acid;  
 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-  
 5-nitrobenzoic acid;  
 2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;  
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-  
 benzoic acid;  
 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-  
 benzoic acid;  
 2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-  
 benzoic acid;  
 2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;  
 5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid.  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-  
 benzoic acid;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
 trifluoromethyl-benzoic acid; or  
 2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid.

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## 21. The compounds:

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-  
benzoic acid;5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic  
acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-  
benzoic acid;10 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic  
acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
methanesulfonyl-benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-  
yl-benzoic acid;15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-  
benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-  
benzoic acid; or20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-  
benzoic acid.

## 22. The compounds:

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-  
benzoic acid;25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-  
benzoic acid;6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-  
benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-  
benzoic acid;30 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-  
benzoic acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-  
benzoic acid;

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-  
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-  
trifluoromethyl-benzoic acid;

10 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-  
trifluoromethyl-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Aminophenyl)propyl]phenylamino} benzoic acid;

15 2-{4-[3-(3-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Aminophenyl)phenylamino} benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino} benzoic acid  
monohydrochloride;

20 2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino} benzoic acid  
monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino} benzoic  
acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino} benzoic  
acid;

25 2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino} benzoic acid;

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-  
ethylamino)benzoic acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

30 2-{4-[2-(3-Aminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino} benzoic  
acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;



thioxothiazolidin-3-yl}acetic acid:

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3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid;

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid;

5 2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methylbenzoic acid;

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulofnamide;

10 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

15 5-Amino-2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

20 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitrobenzoic acid;

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

25 2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

30 2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

30 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-  
benzoic acid;

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3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid;

5 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

10 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isoindol-5-ylamino]-benzoic acid; or

20 2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid.

23. The compounds:

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzoyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

30 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

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2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

or

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid.

24. The compounds:

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

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25. 2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid or a pharmaceutically acceptable salt thereof.
26. 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}benzoic acid or a pharmaceutically acceptable salt thereof.
- 5 27. A compound which is selected from:
- 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid;
- 4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;
- 10 4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid;
- 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;
- {4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine;
- 15 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid;
- 3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;
- 20 2-{4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monosodium;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monopotassium;
- 25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid calcium salt (1:1);
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoate-2-hydroxy-1,1-bis-hydroxymethyl-ethyl-ammonium;
- 30 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-methoxy-benzoic acid;

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2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{3-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(2,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic  
 5 acid;  
 2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(2-Hydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-benzoic acid;  
 10 2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-phenylamino}-benzoic  
 acid;  
 15 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;  
 2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid;  
 2-(3',5'-Dichloro-biphenyl-4-ylamino)-benzoic acid;  
 4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-  
 5-nitro-benzoic acid;  
 20 2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-  
 benzoic acid;  
 5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-  
 benzoic acid;  
 N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-  
 25 C,C,C-trifluoro-methanesulfonamide;  
 N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-  
 benzenesulfonamide;  
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-  
 trifluoromethyl-benzoic acid;  
 30 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic  
 acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

5 2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-5-dimethylamino-benzoic acid;

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-benzoic acid;

10 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid;

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

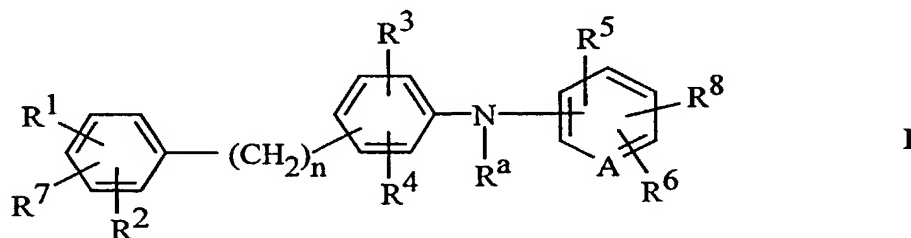
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid;

15 2,2'-[1,2-Ethanediy]bis (4,1-phenyleneimino)]bis-benzoic acid; and

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

28. A method of imaging amyloid deposits, the method comprising:

20 a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



wherein

25

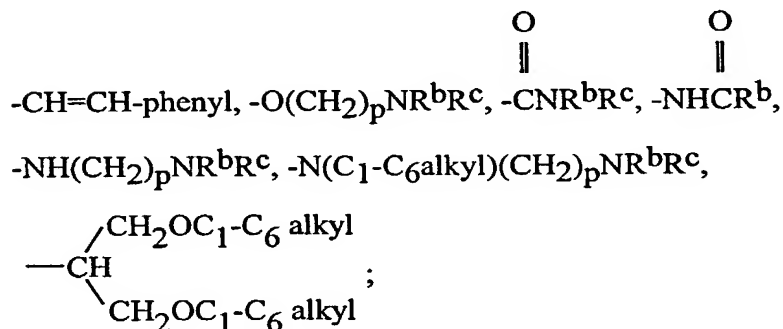
$R^a$  is hydrogen,  $C_1$ - $C_6$  alkyl, or  $-CC(=O)C_1$ - $C_6$  alkyl;

$n$  is 0 to 5 inclusive;



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$R^1, R^2, R^3, R^4, R^5, R^6$ , and  $R^7$  are independently hydrogen, halogen,  
 $-OH$ ,  $-NH_2$ ,  $NR^bR^c$ ,  $-CO_2H$ ,  $-CO_2C_1-C_6$  alkyl,  $-NO_2$ ,  $-OC_1-C_{12}$   
 alkyl,  $-C_1-C_8$  alkyl,  $-CF_3$ ,  $-CN$ ,  $-OCH_2$  phenyl,  $-OCH_2$ -substituted  
 phenyl,  $-(CH_2)_m$ -phenyl,  $-O$ -phenyl,  $-O$ -substituted phenyl,



$R^8$  is  $COOH$ , tetrazolyl,  $-SO_2R^d$ , or  $-CONHSO_2R^d$ ;

$R^b$  and  $R^c$  are independently hydrogen,  $-C_1-C_6$  alkyl,  $-(CH_2)_m$ -phenyl, or

$R^b$  and  $R^c$  taken together with the nitrogen atom to which they are  
 attached form a cyclic ring selected from piperidinyl, pyrrolyl,  
 imidazolyl, piperazinyl, 4- $C_1-C_6$  alkylpiperazinyl, morpholino,  
 thiomorpholino, decahydroisoquinoline, or pyrazolyl;

$R^d$  is hydrogen,  $-C_1-C_6$  alkyl,  $-CF_3$ , or phenyl;

$m$  is 0 to 5 inclusive;

$p$  is 1 to 5 inclusive;

$A$  is  $CH$  or  $N$ ;

$R^1$  and  $R^2$ , when adjacent to one another, can be methylene-dioxy;  
 or the pharmaceutically acceptable salts thereof.

- b. allowing sufficient time for the labeled compound to become  
 associated with amyloid deposits; and
- c. detecting the labeled compound associated with the amyloid  
 deposits.

29. The method of Claim 28 wherein the patient has or is suspected to have  
 Alzheimer's disease.

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30. The method of Claim 28 wherein the labeled compound is a radio labeled compound.

31. The method of Claim 28 wherein the labeled compound is detected using MRI.

5 32. The compounds:

2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid;  
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

10 2-[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; and

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid.

33. A pharmaceutical formulation comprising a compound of Claim 19 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

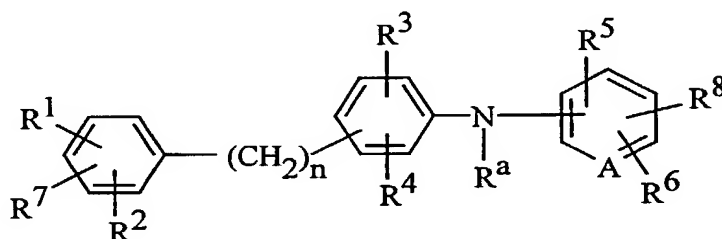
34. A pharmaceutical formulation comprising a compound of Claim 20 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

35. A pharmaceutical formulation comprising a compound of Claim 21 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

36. A pharmaceutical formulation comprising a compound of Claim 22 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

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37. A pharmaceutical formulation comprising a compound of Claim 23 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.
38. A pharmaceutical formulation comprising a compound of Claim 24 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.
39. A pharmaceutical formulation comprising a compound of Claim 25 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.
40. A pharmaceutical formulation comprising a compound of Claim 26 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.
41. A pharmaceutical formulation comprising a compound of Claim 32 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.
42. A compound of Formula I.



I

wherein

R<sup>a</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, or -CC<sub>1</sub>-C<sub>6</sub> alkyl;

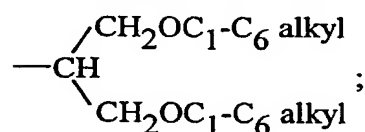
n is 0 to 5 inclusive;

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, and R<sup>7</sup> are independently hydrogen, halogen,-OH, -NH<sub>2</sub>, NR<sup>b</sup>R<sup>c</sup>, -CO<sub>2</sub>H, -CO<sub>2</sub>C<sub>1</sub>-C<sub>6</sub> alkyl, -NO<sub>2</sub>, -OC<sub>1</sub>-C<sub>12</sub>

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alkyl, -C<sub>1</sub>-C<sub>8</sub> alkyl, -CF<sub>3</sub>, -CN, -OCH<sub>2</sub> phenyl, -OCH<sub>2</sub>-substituted phenyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl, -O(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>, -C(=O)NR<sup>b</sup>R<sup>c</sup>, -NHCR<sup>b</sup>,  
 -NH(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>, -N(C<sub>1</sub>-C<sub>6</sub>alkyl)(CH<sub>2</sub>)<sub>p</sub>NR<sup>b</sup>R<sup>c</sup>,



R<sup>8</sup> is COOH, tetrazolyl, -SO<sub>2</sub>R<sup>d</sup>, or -CONHSO<sub>2</sub>R<sup>d</sup>;

R<sup>b</sup> and R<sup>c</sup> are independently hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>-phenyl, or

R<sup>b</sup> and R<sup>c</sup> taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C<sub>1</sub>-C<sub>6</sub> alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R<sup>d</sup> is hydrogen, -C<sub>1</sub>-C<sub>6</sub> alkyl, -CF<sub>3</sub>, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R<sup>1</sup> and R<sup>2</sup>, when adjacent to one another, can be methylene-dioxy; or the pharmaceutically acceptable salts thereof.

43. A pharmaceutical formulation comprising a compound of Claim 42 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

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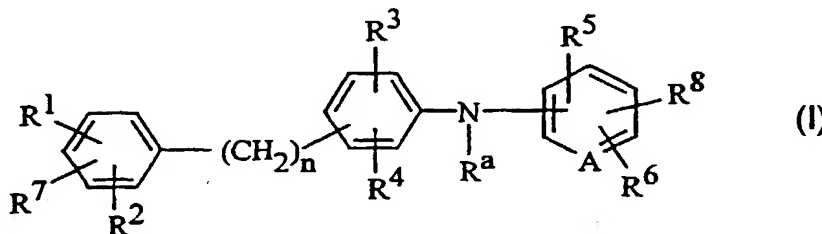
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(54) Title: METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS



(57) Abstract: The present invention provides a method of treating Alzheimer's disease using a compound of Formula (I). Also provided is a method of inhibiting the aggregation of amyloid proteins using a compound of the Formula (I) and a method of imaging amyloid deposits, as well as new compounds of Formula (I).

Express Mail No. EF378134357US

WO 00/76489 A2

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Citizenship		
Post Office Address		

~~Express Mail No. EF378134357US~~Docket No.  
5941-01-DRK

# Declaration and Power of Attorney For Patent Application

## English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS**

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on \_\_\_\_\_ as United States Application No. or PCT International Application Number \_\_\_\_\_ and was amended on \_\_\_\_\_

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

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14

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I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/138,550</u>	<u>6/10/99</u>
(Application Serial No.)	(Filing Date)
<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)
<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

<u>PCT/US00/15071</u>	<u>5/31/00</u>	<u>Pending</u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u>                    </u>	<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u>                    </u>	<u>                    </u>	<u>                    </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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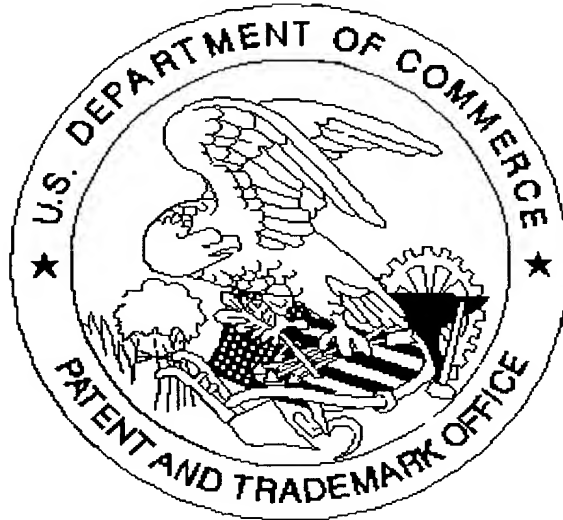
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Eleventh inventor's signature <i>Lary Craswell Walker</i>	Date 12 April 2002
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Thirteenth inventor's signature <i>Nian Zhuang</i>	Date 4/24/02
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Full name of fourteenth inventor, if	
Fourteenth inventor's signature	Date
Residence	
Citizenship	
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